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BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 11 1953

THE NATURE AND PLACE OF THINKING IN MEDICINE*

BY

Sir FREDERIC BARTLETT, C.B.E., F.R.S.

1. The Nature of Thinking

At a first encounter there may seem to be something peculiar about the title of this lecture. Surely it could be said the nature of thinking is the same under all circumstances, and in no way dependent upon its subject matter. This view has, indeed, been held by a great many people, and among them are some excellent psychologists. But it is not to be taken for granted. Even a swift survey, whether of contemporary medical activities or of the history of medicine, is enough to suggest strongly that the fact of the very great diversity of the persons to whom medical discovery and practice offer an overwhelming attraction cannot possibly be accounted for simply in terms of difference of interest in particular medical topics. It would seem that there must be some radical differences between strongly preferred methods of investigation, and that these, in their turn, may be traced to equally radical differences in the process of thinking. Doubtless the differences which I am going to try to discuss can be illustrated in other branches of knowledge as well. But their wide range, as well as the rapidity of change of fashion, of method, and of emphasis to which they have been subjected throughout the whole of their history, makes medical science and practice an outstandingly interesting and fruitful field within which to study the nature and the place of thinking.

Both in ordinary conversation and in technical definition "thinking" is a term which is almost always given an inconveniently wide application. When a man says "I didn't think of that," all that he means is that he failed to give attention to something which was not, in fact, there for him to see or hear, or otherwise to perceive. And most formal definitions which have been framed amount also precisely to this: that there is thinking whenever sensory or perceptual signs or stimuli are supplemented in the course of their observation or discussion in any way whatsoever. Now, there is no known human observation or discussion in which supplementation of this kind does not take place. And so the common view means not only that thinking is present in perceiving—which nobody need doubt—but also that remembering is thinking, and the whole sweep of imagination and fancy is thinking, and believing is thinking. Thinking, in fact, becomes so multiform that it is quite impossible to say anything definite about it at all, except the one formal statement that it is the use of information not immediately sensorially or perceptually present.

If we are to get anywhere effectively we must have more definite starting-points than this, although in a single lecture these will have to be stated in a rather dogmatic manner, and without that experimental justification which is available.

Everybody agrees that thinking is one of the ways that animals have developed for dealing with evidence. Broadly, all human evidence is of two sources—either it comes from direct observation or else it is in some form of record, sometimes descriptive, but more often in the mode of an achieved generalization presented for acceptance or criticism. The first is the only original source, and it requires sensorial perception. When evidence of this sort is fairly examined the striking thing about it is its partial and fragmentary character. At no stage is animal observation a literal and complete reduplication of the external environment upon which it works. The character of the sensory and perceptual mechanisms through which it is made renders such reduplication impossible. Moreover, every great step in advance of animal observation has been less in the service of the accurate and complete reduplication of the external signs and stimuli and more in the service of extending the range and increasing the amount of available evidence, and especially of the building up of information on evidence. It is exceedingly likely, for example, that human observation is less accurate and less complete, relative to its possible range, than that of more primitive and restricted forms, where the sensory mechanisms are fewer and much less specialized. However this may be, all the evidence that is directly accessible comes to us fragmentary and scrappy to a degree. It is full of gaps, and we must try to fill up the gaps. Sometimes—there are innumerable cases in clinical diagnosis and in all kinds of experiments—we have evidence, and then a gap, and then more evidence. We must interpolate. Sometimes, as in clinical prognosis, there is evidence and the evidence stops short and we must extrapolate. We can interpolate or extrapolate, if we like, in the interests of what is often called aesthetic satisfaction, or we can do either or both under the dominance of objectivity—that is, in such a way that the issue we reach can be identified by observation, or proved in accordance with the nature of the system within which we are working. Thinking chooses the second, the objectivity-dominated way.

*A lecture given to the British Postgraduate Medical Federation at the London School of Hygiene and Tropical Medicine on January 27.

Thinking also usually, though not invariably, requires a number of steps or links, and when it does each step must be such that it reduces the number of possible next steps, until eventually, sometimes quickly, sometimes after a protracted process, a stage is reached beyond which all thinking persons will proceed uniformly.

That the kind of process which I have just described briefly does take place when people are given fragmentary evidence and required to bring it to an objective issue can be experimentally demonstrated. That it is the kind of process which all people who have used the term "thinking" rigorously have intended to indicate seems at least to be extremely likely.

This, however, is a lecture on thinking in medical science, and so without any more discussion I propose to try to see what direction this somewhat general lead can give to a study of *the Nature and Place of Thinking in Medicine.*

2. Everyday Thinking in Medicine

First I want to consider the psychological processes involved in certain relatively simple cases of thinking, very common and necessary as I understand them, in medical practice. I shall call this "everyday thinking."

When a "man in the street" is confronted with fragmentary evidence, say about current events, and is required to bring it to an issue, more often than not he will do it by accepting or adopting some generalization, because somebody that he trusts has said so or because it has prestige within his social group, and immediately identifying the evidence as an instance. The issue is then little or nothing more than a restatement of the generalization in terms of the particular evidence.

There seems no good reason to refuse to call this "thinking." At any rate, it certainly is what passes for thinking in most of us most of the time. It does consist in filling a gap between the generalization which is accepted and some concrete evidence which has to be directly examined. It is, basically, the process of at least some of those doctrines of "physical signs" which have received much support in medical practice from time to time.

Or perhaps an instance is the recorded statement of Ambroise Paré when he was asked if the wound of the King of Navarre was mortal. "Yes," he said, "because all wounds of great joints, and especially contused wounds, are mortal according to all those who have written about them."

From our present point of view we need not be much concerned with the generalization or formulated principle which is involved. It is sufficient to notice that this is simply accepted and may be believed. The critical part of the process lies in the treatment of the concrete evidence. For in a great many instances this evidence will lack some of the characters that are required to put it into a general class, and in practically all instances it will possess other characters. The whole process thus depends on observing or, in many cases, assuming points of similarity and ignoring differences. The interesting thing is that for anybody who relies solely on direct observation differences stick out much more prominently than similarities, and are much easier to observe. But once we have accepted a principle the situation is radically changed, and it becomes increasingly easy to slur over differences. Consequently the integrity of thinking in this simple kind of case depends almost entirely upon a determined, and usually conscious, effort to observe and weigh differences, and it is this quality in observation, to give due weight to differences, which needs above all else to be stressed in relatively routine diagnosis. No doubt extreme instances of what can happen when it is ignored are the eighteenth-century theories of "large and small" doses associated with the names of John Brown and Samuel Hahnemann.

Or, again, though maybe it is unfair to treat this as an instance of medical diagnosis, there was the driver of an ambulance wagon in the American Civil War. He was asked if he knew how to treat wounded men. "Oh, yes," he said; "if they are hit here"—pointing to his abdomen—"knock 'em on the head; they can't get well." Any preoccupied medical practitioner who is forced to make rapid routine diagnosis is always up against this difficulty, the psychological source of which is the power of principle to obscure differences, and there seems to be only one real remedy, the development of an experimental approach. We must therefore go on to consider and attempt some analysis of

3. Experimental Thinking in Medicine

Experiment is still often regarded as a kind of abrogation of thinking. Every medical student must have been told of John Hunter's advice to Jenner, "Don't think, but try; be patient, be accurate," or, in an alternative version: "Why think? Why not try the experiment?" But Hunter's own practice, and Jenner's, too, show clearly that the warning was simply against the pitfalls of the kind of thinking that we have just been considering. I believe it can be shown that experimental thinking is different in important respects from the kind which I have called "everyday."

Perhaps there are two sorts of scientific experiment. One, usually the earliest kind to occur, is when some large topic or field of knowledge is well known to be inadequately mapped out, and somebody decides to try to improve ordinary unassisted processes of observation by special methods of recording which will make the detection and interpretation of likenesses and differences in arranged cases that come within this topic more exact and certain. The other, more limited and directed, usually begins when somebody decides to take seriously certain differences revealed by direct observation between specific instances and accepted principle. The kind of thinking required is pretty well the same in both, but the first tends to grow into the second, which becomes both more common and more fruitful as specialization advances. I propose, therefore, to take a fairly simple case of the second kind—probably simplifying it more than is right for the purposes of rapid discussion—and to try to bring out its leading characters as an illustration of experimental thinking.

When Sir James Mackenzie was a young medical practitioner he wrote, "I set myself the task of finding out the nature of the symptoms and signs I met with in the course of my practice. This placed before me two definite objects at which to aim—(1) the understanding of the mechanism of symptoms, and (2) the understanding of their prognostic significance." In this general statement there are two points of importance: the first a resolve to take direct observation seriously, and the second that observations of medical significance must inevitably fall into time-related sequences with gaps that must be filled in. The general resolve, however, had to become more specific. A few years later the death of a patient from heart failure directed Mackenzie's attention to the disorders of circulation, and especially to irregularities of the pulse. At that time any form of pulse irregularity tended to be regarded as serious.

The story of Mackenzie's investigations is already well known. First came the improvement of direct observation by the systematic use of instrument tracings. Then came the first critical step: the comparison of two sources of direct information, sphygmographic and jugular tracings which so far had not been combined for practical purposes, leading to the separation into a special group of those forms of irregularity alleged to be due to a premature beat of the ventricle. There followed the recognition that these also must not be lightly placed all into one class, leading eventually, after about ten years of observation and thinking, to the separation of that form of arrhythmia in which the absence of the auricular wave in jugular tracings was associated with the disappearance of the presystolic murmur, to the reinstatement of a sensible form of digitalis therapy,

and finally to a radical revision of the significance of heart murmurs which had already been studied and described over and over again, and to the view that in the end the only thing that matters is the reserve power of the heart muscle.

It is already an old story, and of course much of it has been rewritten since, but the course of Mackenzie's investigations does bring out very well some of the leading characteristics of experimental thinking in medicine.

First comes the firm resolve not to be swept away by the slumping power of established generalizations, but to give the direct evidence a fair chance. This means almost always that unaided observation must be supplemented by instrumental records. As soon as this is done differences between cases will at once, and, so to speak, by their own inherent capacity to attract attention, spring into prominence. This is only a first step. Differences of themselves lead nowhere, but hidden within them may be some significant similarities which have to be searched for, for they are inherently as difficult to identify as differences are easy. Almost always, perhaps always, they are found only when two or more sources of evidence or of information which so far have never been effectively combined are brought together. This identification of significant likeness or agreement, coupled with an appreciation of differences but a determination not to be controlled by them, is really the crux of the whole thinking activity in the case of the experimental investigation. There is, however, a third characteristic, important in all biological experimentation, but probably more vital in medicine than anywhere else, and this is that the direct sources of information which are used must all be treated as related in a sequence in time and proceeding towards some point which can be treated as terminal. This consideration leads us at once to the third kind of thinking, different in its nature from the other two, far more difficult to understand, and more fascinating to study; namely, to

4. Prognostic Thinking

Perhaps it is not too much to say that all really characteristic or specific medical thinking started in a recognition of the importance of prognosis. "I hold," said Hippocrates, "that it is an excellent thing for the physician to practise forecasting." All the great clinicians have said much the same, though it is less fully recognized that prognosis is equally a part of medical experiment, and that when general biological experiments turn out to have a medical significance it is because their conclusions are viewed in the light of some prognostic approach.

On the whole there seems to have been very little direct and sustained attempt to discover and understand the processes which are internal to medical prognosis. They are perhaps most frequently supposed to depend upon continuous faithful observation and accumulated experience. "No doctor," said James Mackenzie, "lives long enough to write a reliable book on prognosis." He was himself no doubt a fine clinician, but the idea behind this assertion seems wrong. Prognosis is often, at the least, a swift process, though its confirmation may be slow enough. On the whole I think that the great prognostic physicians have shown their special facility early, just as they have also been far more successful with the particular case than with their generalizations from many cases.

There seems to be something about medical prognosis not unlike expertness in games. At some stage the games expert seems pretty well sure to attempt an analysis of his expertness, and then he will write things like the tortuous books on golf, or cricket, or lawn tennis. The elaborate post-mortem examination gets cluttered up with detail which has minor importance, if any at all, at the living moment of performance. And this may be more than an analogy, for there is something about prognosis identical with the technique of the surgeon. Sir James Paget, speaking of William Fergusson, referred to his hands, "which were so strong and yet so sensitive, so swift and light," so apt to "clear and prompt invention." There is something executive about prognosis that seizes, so to speak, the chance of the moment. It is observation of direction, and what that is still remains a psychological puzzle as yet unravelled.

There are great differences between extrapolative thinking in mathematics and the physical sciences and extrapolative thinking, of which prognosis is obviously an example, in biology and medicine. In the former the elements which have to be used are known; their properties are known, too, and the relations of those properties can be defined at the beginning and do not change. But in the latter the elements which are to be used must be picked out of a lot of others, all of which may at first seem to have an equal status. We cannot enumerate the properties of the elements completely, and especially we do not know at the beginning what are their relations. We have to inspect instances, and, basing ourselves always upon agreements and differences, reach an issue through an appropriate use of these.

However, prolonged extrapolative thinking does, of course, take place in mathematics, the main difference perhaps being that in the mathematical case the issue is more or less defined to begin with, whereas in medical prognosis it has to be extracted from the direct evidence just as much as the items of evidence which are going to lead up to it. As is well known, Poincaré and Jacques Hadamard, in particular, have made penetrating studies of mathematical extrapolation. There is one suggestion of Hadamard's which seems to me to be particularly interesting. He is discussing Barnard's statement that "those who have an excessive faith in their own ideas are not well fitted to make discoveries." He says that this is not very important in mathematics, because good mathematicians when they make errors soon perceive and correct them. "As for me, I make many more of them than my students do; only I always correct them so that no trace remains in the final result. The reason for this is that, whenever an error has been made, insight—that scientific sensibility . . . —warns me that my calculations do not look as they ought to."

Can this suggestion be taken over directly into the biological field of medical prognosis? If we do this we have to suppose that the directional character which is always present in vital evidence can be known, or perceived, only, or mainly, through a greatly enhanced sensitivity to wrongly assigned directions. I see no reason to doubt that this does happen, but that it is the whole story, or even a main part of it, seems exceedingly unlikely. I know of no outstanding recorded instance of medical prognosis in which the final verdict was reached through the progressive rejection of all possible, or even of a large number of possible, errors. What, then? Are we reduced to the view that the directional character of evidence gathered from the examination of a patient is immediately perceived, or known, by some process of immediate insight or intuition about which nothing more can be said?

I believe that the whole of this matter could be brought to the test of reasonably controlled psychological experiment. But the experiments have not been carried out, and all that I can do now is to make certain suggestions in an extremely tentative manner.

No medical prognosis is achieved on the basis of a single examination. When this appears to be done it is only because the physician has already a fund of information, based upon other examinations, about the signs and symptoms which his direct observation has identified. Moreover, the symptoms and signs are never seen in isolation, never merely enumerated; they are seen as carrying trails which run off into the contemporary life setting, and in most cases also into the course of individual history. This being so, it seems to me very likely that prognostic thinking has fundamentally the same character as the thinking involved in scientific discovery. This is a refusal to accept apparent differences at their face value, and a capacity to probe beneath them in order to find out whether there are significant likenesses. In the case of the prognosis, the observation and information made or used are sections of

an individual life stream; in the case of scientific discovery they are more commonly fields of fact or of knowledge that are to a more superficial examination separate. In the first the resemblances are essentially of changing phenomena in temporal process. In the second this is less often the case. The essence of both is a persistent search for uniformities and likenesses where differences abound. Success in both is difficult and somewhat rare, principally because our human apparatus for building up factual observation and knowledge makes the appreciation of differences among similarities relatively easy, but of similarities among differences relatively hard.

If this is even broadly along the right lines the main reason for one thing which will impress itself upon everybody who studies the history of medicine will become more clear. All the great doctors, especially the clinical physicians, have been men of wide and varied interests and have used them all. They have put their need for this in different ways according to the different times in which they have lived, but it is a theme that crops up again and again. "The doctor," said Paracelsus, "must be a traveller because he must inquire of the world." Osler was for the peripatetic professorship, the quinquennial rejuvenation by return to hospital and laboratory, the bedside library by no means to be restricted to medical writing. Only the man of many and related interests is likely to find those uniformities in nature and in human life which he must use to fill up the gaps of observed and recorded evidence, in ways that pass unnoticed by the mass. This process of bringing together fields or items of knowledge and observation which hitherto have been unrelated is almost always the first step of discovery, especially in biology. Since in a sense every exercise in medical practice is a voyage of discovery, the vital value of varied interests is never to be overlooked.

5. The Conclusion

I have said that thinking is the expansion of evidence in accord with the evidence, to fill up the inevitable gaps in evidence. The gaps are so filled that either at once, or through a series of steps, a stage is reached beyond which all persons who accept and remain loyal to the evidence must reach the same objective issue. Since all medical science and all medical practice claim a direct evidential basis, and since our human mechanisms for dealing with evidence cannot avoid fragmentariness, thinking has its essential place in absolutely every medical exercise, whatever its level, and whatever its generality or individuality. There are some activities required in everyday life, especially probably in much current industrial practice, where all that is required is simply to treat each particular case as it comes along as nothing but a fresh instance of an already defined class of cases. Then the decision, and the resulting action, if there is any, can fairly be called automatic or mechanical. If there is any genuinely routine diagnosis it has this same character, but it is doubtful whether there ever can be, and so the physician can never get away from the challenge to think.

But the *nature* of medical thinking does differ in different instances. In so far as routine diagnosis is approached the success of the whole thing depends upon the identification of similarities combined with a resolute refusal to neglect differences. And it is the latter that is apt to be difficult.

Once the function of the observed differences becomes clear, either for the purpose of individual diagnosis or for the general development of medical science, the first step is usually to supplement the deficiencies of direct unaided observation by the invention and use of instrumental recording. Experiment comes upon the scene, and must play a greater and greater part as time goes on. But in first-hand observation the difficult thing is the identification of likenesses. So inherently difficult is this that once experiment starts it inevitably develops in the direction of limited range and specializations which separate one branch of knowledge or topic of exploration from another. Practically all biological discovery, however, whether it concerns the individual instance or the establishment of general principles of treatment and explanation, rests upon the combination of different specialized fields of evidence. Thinking then is apt to be effective only when the thinker has many interests and is able to combine them. Always the watchword or slogan is "Search for likenesses, especially in unexpected places."

All medical phenomena have a future as well as a past, and their significance at any stage is as much determined by what lies ahead as by what has already happened. When this becomes dominant we have prognostic thinking, the mechanism of which is still hardly at all understood. Perhaps it depends upon some unusual sensitivity to those lines of exploration which are not likely to be very fruitful, or perhaps there is something more positive about it: the direct identification of lines of interpretation which will reach an issue. We call this insight. But it may be a capacity to use memory and stored experience, and at the same time to stay loyal to direct observation; so that likenesses which are embedded in a mass of differences and very likely to escape attention are given fair weight. If so, insight, intuition, wisdom, good judgment, are as analytical in their nature as any other thinking processes.

The doctor, like any other thinker, is all the time using "signs." The items, and the established principles, of evidence are used to carry him into the gaps in evidence. If we could know what these signs are we should be in a better position to understand the internal mechanism of thinking. And if it turned out that there are signs which the doctor must use, and which are not used much or at all anywhere else, we could perhaps say whether his thinking is peculiar in its internal mechanism. This seems very unlikely. It is certain that the signs need not be words at any level of medical thinking. It seems likely that the medical scientist and the physician can use effectively any, or all, of the signs open to any other person: words, or images, or perhaps immediately apprehended "directions." Until we know a lot more about this the attempt, not uncommon nowadays, to be dogmatic about the internal, particularly the central nervous, mechanisms of thinking, whether for medicine or for any other field, seems to be premature.

A recent account published by the National Joint Industrial Council for the Rubber Manufacturing Industry summarizes the accident experience of a considerable part of the British rubber industry from January, 1950, to June, 1952. In this period more than 26,000 reports of accidents were received; they varied from those causing trivial injuries to those with disastrous results. The authors of this enterprising study have not only shown how accidents arise in the rubber industry but indicate how wide and useful may be the application of similar methods of investigation elsewhere. They emphasize need for accuracy in classification: far too many accidents, many of them severe, come under the general heading "Other Cause." A high proportion of the accidents were found to be not specific to the conditions of the industry and its machinery but to be in two groups—"Persons Falling" and "Falling Material"; these account for 40% of the serious accidents. Some of the figures, however, are of questionable value. For instance, the fact that more men than women were injured in certain types of accident is of no interest unless the numbers of each at risk are known. One practical result of the survey has been a substantial drop in the frequency of accidents in the industry. The important role of the foreman in keeping workers alert and careful is emphasized. The authors state that "goggles can give positive protection, and the men who need their protection really must accept them." Unfortunately, they do not. Perhaps only legal sanctions and fear of dismissal can make rules observed, though much can be achieved by education, competition, and good morale.

A RELATIONSHIP BETWEEN CANCER OF STOMACH AND THE ABO BLOOD GROUPS

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It was shown by Stocks (1950) that the standardized mortality of cancer of the stomach tended to be greater in northern than in southern towns in England. Stocks considered this to be consistent with the hypothesis that gastric cancer depends on an irritant. The only environmental factor which appeared to correlate in any way with the varying incidence of cancer of the stomach was hardness of water, towns with a water supply of moderate hardness tending to have lower rates than towns with soft or very hard water. This correlation was not a very close one. He showed also that the standardized mortality of cancer of the stomach was greater in towns with a low proportion of people of advanced age and in towns with a high proportion of men in unskilled and partly skilled occupations. Stocks did not explore, and apparently did not take into account, any possible genetic difference in the populations which he examined, nor was this possibility mentioned by Legon (1951, 1952) in attempts to correlate the geographical variations in the mortality from gastric cancer with variations in the organic content of the soil.

It occurred to one of us that there might be a correlation between the high northern incidence of cancer of the stomach and the genetic differences which are reflected in the ABO blood groups, the frequency of blood group O being greater, that of A less, in northern than in southern populations, B and AB being similar in all geographical areas in England and Scotland.

Previous published work on the association of the ABO blood groups with cancer has been on very small series of cases without adequate controls. The results have been diverse and without statistical significance (Alexander, 1921; Johannsen, 1925; Goldfeder and Fershing, 1937).

Method

A collection was made of cases of cancer of the stomach from a number of hospitals in England and Scotland, and the distribution of the ABO blood groups in patients with stomach cancer from each hospital was compared with the distribution of ABO blood groups in an equal number of patients chosen at random from the same hospital. The criterion of diagnosis has in most cases been a histological report on material obtained at operation or post-mortem examination, but in a few cases we have been dependent upon "a cast-iron clinical diagnosis based on radiological findings, operative findings, and clinical follow-up." Our survey concerns only cases treated in the past five years, for in most hospitals blood grouping has been dependable and accurately recorded only during this period. In most cases the blood groups have been determined by hospital laboratories, though in a very few cases the determinations have been made in the laboratory facilities of a clinical unit. Wherever possible, cross-checks against the case records were obtained from the hospital transfusion service.

For controls we have selected, where possible, a cross-section of the patients of the hospital concerned rather than data from the regional transfusion organization, since the hinterland of a hospital has not necessarily the same population as that served by the transfusion service. This type of control has been used in all the provincial and Scottish hospitals which we have approached, with two exceptions. In these two exceptions controls were not easily obtainable from the hospital population, and in the case of these, affecting 566 of our controls, the blood groups of an equal control number were estimated from their frequencies in very large numbers of the local population obtained from the local transfusion centre. In the London area we have used as controls the blood-group frequencies in a series of 10,000 from North-west London collected and published by Discombe and Meyer (1952). These frequencies are very close to those given by Fisher and Taylor (1940) for Southern England.

Results

Our results are presented in simple form in Table I, and are analysed statistically by Dr. Fraser Roberts in Table II. It is clear that throughout England the distribution of blood groups in cancer of the stomach is different from their

TABLE I.—*Percentage Distribution of Blood Groups in Cases of Stomach Cancer Compared with that in Equal Numbers of Controls*

	Cancer Cases				Controls			
	O	A	B	AB	O	A	B	AB
Newcastle (101 cases) ..	43·6	43·6	11·9	1·0	52·5	37·4	7·6	2·5
Leeds (217 cases)	42·4	47·9	7·4	2·3	46·5	40·3	7·1	6·2
Manchester (771 cases) ..	44·7	44·5	6·4	3·8	52·1	38·4	7·0	2·5
Liverpool (217 cases) ..	39·2	44·7	12·4	3·7	49·7	39·6	7·8	2·7
Birmingham (100 cases) ..	37·0	57·0	3·0	3·0	49·6	44·4	3·0	3·0
Total of Northern England (1,406 cases) ..	42·9	46·4	7·6	3·1	50·7	39·3	6·8	3·2
London (1,340 cases) ..	43·1	46·0	7·9	2·9	45·8	42·2	8·9	3·1
Scotland (478 cases) ..	51·2	36·4	9·6	2·7	52·6	32·5	11·7	3·1
Overall* figures (3,632 cases)	44·5	44·8	7·8	2·9	48·6	39·8	8·3	3·2

Gene Frequencies†

London		Northern England		Overall English + Scottish*	
Cancer	Control	Cancer	Control	Cancer	Control
p=0·287	0·261	0·290	0·236	0·278	0·243
q=0·058	0·064	0·056	0·047	0·056	0·058
r=0·657	0·678	0·655	0·713	0·668	0·698
1·002	1·003	1·001	0·996	1·002	0·999

* The overall figures are the sum of Northern England, London, Scotland, and four other scattered hospitals in the south of England (the latter individually too small for deductions but included for completeness).

† Calculated from nomograms published by Boyd (1937-8).

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distribution in the general population in England, and this difference is highly significant. Blood group A is more frequent, blood group O less frequent in patients suffering from cancer of the stomach than in the general population of the same locality. In every hospital from which data were obtained this same difference was observed. There thus seems to be a direct or indirect correlation between the A and O groups and susceptibility to cancer of the stomach in this country.

Discussion

Since cancer of the stomach is commoner in the North of England than in the South, while group A is less common in the North of England than in the South, it follows that this correlation with the blood groups is not responsible for the geographical differences in the incidence of cancer of the stomach demonstrated by Stocks. We must postulate that there are at least two influences operating in the cause of cancer of the stomach in England. One is an inherited influence with a relation to the A and O blood groups. The other, presumably environmental, must be assumed to be responsible for the high northern frequency of carcinoma of the stomach which Stocks showed. Since group A is commoner in the South of England than in the North and is more frequent in the cancer of stomach patients, it follows that the inherited factor operates in a direction opposite to the environmental factor of Stocks with regard to the geographical distribution of cancer of the stomach in England. Because of the low frequency of group A in the North of England, cancer of the stomach should be less common there than it is in the South, while Stocks has shown that it is in fact more common. Our figures thus add weight to the importance of the environmental factor which Stocks has postulated.

Any explanation of the apparent susceptibility to cancer of the stomach with which blood group A is invested, or protection against cancer of the stomach which is afforded by the possession of blood group O, is exceedingly difficult. It is clear that the susceptibility to cancer of the stomach or the protection against cancer of the stomach which our figures suggest must be inherited, since blood groups A and O are inherited. Our preliminary interpretation of the data was that they revealed high-incidence and low-incidence strains in the population of England with respect to cancer of the stomach. Such a hypothesis, however, would be difficult to substantiate in the light of the known facts of Britain's genetic history. The essential difference between patients with cancer of the stomach and controls affects blood groups O and A in a reciprocal fashion, B and AB retaining an equal level in both groups throughout. This reciprocity between O and A, and the constancy of B and AB, which are characteristic of the ethnological pattern of the population in this country, do perhaps strengthen an anthropological (i.e., ethnological) hypothesis. It would still be difficult, however, to devise a genetic explanation for the correlation of the blood groups with cancer of the stomach based on the known ethnological origins of the population of this country.

The alternative explanation would in its turn offer difficulty to the pathologist. It is hard to conceive any mechanism whereby the antigen A could offer a slight but definite susceptibility to, or the antigen O offer a slight but definite protection against, such a disease as cancer of the stomach. Further speculation would appear to be unprofitable at this stage. Extension of the data to cover other forms of malignant disease and other populations ethnologically alien to ours might make it clear whether an ethnological or a serological hypothesis is more tenable.

Some other conclusions may be drawn from our figures. It is generally assumed that the ABO blood groups have no selective value, at least in adults, the possession of any one of the groups conferring neither advantage nor disadvantage on its possessor with respect of survival. Our figures would seem to show that blood group A has in England at least a negative selective value, blood group O a positive selective value because of the greater and lesser risk of cancer of the stomach which they respectively offer. Admittedly cancer of the stomach most often affects individuals after their most active reproductive period, and the transmission of the gene for group A is in most cases not prevented. Nevertheless, cancer of the stomach does affect younger people on occasion, and blood group A must therefore be regarded as having some negative, and blood group O some positive, selective value, however slight.

It is possible that there is some intermediate influence affording an indirect rather than a direct correlation between these blood groups and cancer of the stomach. Achlorhydria and pernicious anaemia, for example, come to mind as possible links.

Cancer of the stomach is commoner among the unskilled and semi-skilled than among the professional and clerical orders. We have attempted, but failed, to find a method to correlate blood groups with social class. It seems unlikely that in this country there should be differences of blood-group distribution in the various social orders, and Fraser Roberts (1953) has informed us that no such class difference appears to exist in at least one English locality.

The inheritance of cancer of the stomach has been previously suspected. One need only mention the Bonaparte family in this connexion.

Further evidence could be obtained from studies on the incidence of cancer of the stomach in twins. Gorer (1937–8) reviewed the literature on cases of cancer of all sites occurring in twins. He recorded four pairs of monozygotic twins and one pair of dizygotic twins of which each pair developed cancers of the stomach either simultaneously or within a year of each other. He concluded : (1) that heredity and environment should not be regarded as alternative causes of cancer, and that genetic factors must be regarded as influencing the sensitivity of individuals to stimuli capable of giving rise to malignancy ; (2) that evidence obtained from studies with pure lines of mice shows that such genetic factors can be of great importance but do not fix the time at which the tumour will appear ; (3) the likelihood of obtaining simultaneous development of identical tumours in man is probably much lower ; and (4) that tumours of the alimentary canal, and especially the stomach, appear to be influenced by genetic factors.

Our findings would seem to substantiate that inheritance plays some part in the susceptibility to or protection against cancer of the stomach. The data respecting twins suggest that susceptibility is more important in this connexion than resistance.

We have explored a little the geographical and ethnological aspects of the correlation between blood groups and cancer of the stomach beyond the British Isles, but the collection of data is difficult. We have, however, obtained with the help of Dr. Holländer and his Swiss colleagues the most striking figures from Basle, where the incidence of blood groups in 704 cases of cancer of the stomach is O 36.22%, A 53.12%, B 7.53%, AB 3.13%, while in 4,518 controls from the general population the frequencies are O 41.65%, A 45.06%, B 9.03%, AB 4.26%. These differences are highly significant.

Certain North American Indian tribes have a very high incidence of group A indeed. If it could have been shown that they had also a high incidence of cancer of the stomach the hypothesis that predisposition to or protection against cancer of the stomach depended directly on an antigenic or a serological factor would be greatly strengthened. The American Bureau of Indian Affairs has assisted us in this matter, but the Indian tribes with high incidence of group A are so small, and their expectation of life is so low, that figures about cancer of the stomach are not available.

This technique of examining the distribution of blood groups in a disease is capable of further extension. It could be applied most conveniently to those diseases which require blood grouping for their treatment by transfusion, or which are commonly submitted to an operation which requires transfusion. We propose to examine cancer of the rectum, cancer of the colon, cancer of the lung, brain

tumours, and the blood dyscrasias with particular reference to pernicious anaemia, and peptic ulceration for other possible relationships with the blood groups. In view of the virus work of Bittner it would be desirable to apply the method also to cancer of the breast, though transfusion is seldom required for a patient submitted to radical amputation of the breast, and a large enough series might be difficult to collect.

Statistical Analysis

It is clear that there is practically no difference in the proportions of those with gene B for England and Scotland : $\frac{(B + AB)}{(O + A + B + AB)}$ = 11.08% and 11.57% respectively. The Swiss data do show a difference—10.65% and 13.28%—but this is not significant : χ^2 (with Yates's correction) = 3.504. What the British data do show is a reciprocal difference in the relative proportions of O and A. Hence the simplest and most straightforward analysis is to examine the ratio $\frac{A}{(A + O)}$. This is done in Table II. The conclusions are clear. The total χ^2 for the difference in $A/(A + O)$ between cancer patients and controls is enormously significant, $P<1/10,000$, and the seven separate areas are perfectly homogeneous in this respect.

TABLE II.—*Analysis of Differences in Relative Proportions of Groups O and A in Cancer Patients and Controls*

1	2	3	4	5	6	7	8	9
	Cancer Cases		Controls		A/(A+O)%			
	O	A	O	A	Cancer	Control	Diff. Cancer-Control	χ^2
Manchester ..	343	349	402	295	50·43	42·32	+8·11	9·183
Liverpool ..	85	97	108	86	53·30	44·33	+8·97	3·022
Leeds ..	92	104	102	87	53·06	46·03	+7·03	1·902
Birmingham ..	37	57	50	44	60·64	46·81	+13·83	3·616
Newcastle ..	44	44	53	37	50·00	41·11	+8·89	1·418
London ..	578	617	614	565	51·63	47·92	+3·71	3·267
Scotland ..	245	174	252	155	41·53	38·08	+3·45	1·022
Total ..	1,424	1,442	1,581	1,269	50·31	44·53	+5·78	19·198

Col. 9: χ^2 separately from the eight 2×2 tables.

Analysis	D. of F.	χ^2
Sums of χ^2 for seven areas separately ..	7 ..	23·430
Total for England and Scotland	1 ..	19·198
Difference attributable to heterogeneity ..	6 ..	4·232

As might be expected, weighting makes practically no difference. The mean difference becomes +5.80 instead of +5.78, and the χ^2 for heterogeneity 4.121 instead of 4.232.

The frequencies in the controls correspond reasonably with what would be expected in the regions concerned. Fisher and Taylor's (1940) figure for $\frac{A}{(A + O)}$ for the South-east of England is 48.8, against that given for London in the present paper of 47.9. A figure of 45.5 would very fairly represent England east of the Pennines over an area stretching from Leeds, Bradford, and Hull to Newcastle-upon-Tyne. The northern area controls give 43.4. Thus the ratios for controls are lower than expectation, though only slightly so; in any event the ratios for the cancer series are far higher than those for the corresponding general populations.

Conclusions

The frequency of blood group A is greater and the frequency of blood group O less in patients suffering from cancer of the stomach than in the general population of the locality in which they live.

From this correlation of blood groups and cancer of the stomach it follows that there is an inherited element in the susceptibility or to protection against cancer of the stomach.

This inherited element is not responsible for the known geographical differences in the incidence of cancer of the stomach in England.

The environmental element which Stocks has postulated in the aetiology of cancer of the stomach is more potent than would appear from the geographical incidence of the disease in England.

It is not possible from our present data to deduce whether the relationship between blood groups A and O and cancer of the stomach is dependent upon high- and low-incidence strains of cancer of the stomach in the general population of Great Britain or upon some specific effect of the antigens A and O.

In view of the relationship with cancer of the stomach in Great Britain it is no longer possible to regard blood groups A and O (in adults) as being devoid of selective value.

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Ciba Laboratories have recently presented a film on senile obliterative arteritis of the legs to the B.M.A. Film Library. The course, diagnosis, and management of the condition are demonstrated by members of the university surgical unit, Manchester Royal Infirmary. The film is a 16-mm. colour film with commentary, and it runs for about 55 minutes. It is divided into three parts : the first deals with the pathological anatomy, the second with clinical examination, and the last with the general and local management of intermittent claudication and severe ischaemia. The producer was Dr. Brian Stanford.

SYMPTOMATIC DISTURBANCE AFTER SINGLE THERAPEUTIC DOSE OF X RAYS

ITS RELATIONSHIP TO THE GENERAL RADIATION SYNDROME

BY

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The development of atomic power and the consequent dangers, both in war and in peace, of exposure to the radiations produced by nuclear fission have instigated extensive research into the effects of whole-body irradiation on many animal species. This research, together with the observations made on the populations of Hiroshima and Nagasaki following their exposure to the radiations of the atomic bombs, has shown that such irradiation produces a fairly well defined pattern of signs and symptoms, collectively known as the general radiation syndrome (Fig. 1). This syndrome has been reproduced following whole-body irradiation given to a wide range of mammals such as rats, mice, monkeys, dogs, swine, etc., and, although there are certain species differences, particularly concerning the critical dose of *x* rays required to produce the full syndrome in each instance, the overall picture of the syndrome is surprisingly comparable throughout the range of mammals investigated. The fact that such a reproducible syndrome exists is of great value and importance in furthering basic research work into physiological disturbances produced by *x* rays.

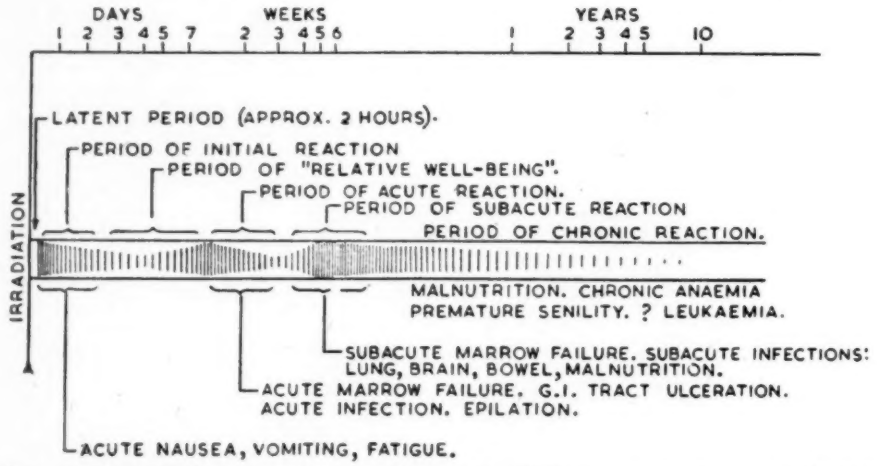

FIG. 1.—Diagrammatic representation of the general radiation syndrome in man. (Adapted from Liebow, Warren, and De Coursey, 1949.)

Walsh (1897) first described acute constitutional symptoms in an *x*-ray worker, and since that time many reports have appeared concerning the production of such symptoms as nausea and vomiting in patients undergoing radium and *x*-ray therapy. Early workers held several factors to be responsible for these symptoms, among which may be mentioned poor ventilation of the treatment rooms, electrical charging of the patient's body, psychological disturbances, and the release into the circulation of the toxic products of protein breakdown. The position to-day regarding the aetiology of these symptoms is only a little less confused. Progress has been hampered by the lack of any clear-cut definition in the medical literature of what has come to be known to radiotherapists as radiation sickness, and the apparent absence of any correlation with the disturbances found after the experimental whole-body irradiation of animals.

It is the object of this communication to describe the pattern of symptoms which occurs in human beings shortly after a single exposure to a dose of *x* rays within therapeutic limits, and to demonstrate the place of this pattern within the general radiation syndrome.

Clinical Material

Concurrently with the supervision of the *x*-ray therapy of certain patients referred to the Radiotherapy Department of Hammersmith Hospital, detailed clinical observations were made before and after a single dose of *x* rays. Fifty such patients have now been observed, and they were selected for these studies because their general health was good and the nature of their disease necessitated the irradiation of a large volume of tissue. The primary diseases of these patients are as follows:

Ankylosing spondylitis	20
Reticulosis	20
Carcinoma of ovary (post-operative)	5
" " testis "	2
" " thyroid "	1
Malignant melanoma (recurrent)	2

It will be seen that the majority suffered either from ankylosing spondylitis or from various forms of reticulosis. In the latter group all patients except one have been early or moderately early cases of Hodgkin's disease, follicular reticulosis, and reticulum-cell sarcoma, the single exception being a case of multiple myeloma. The patients suffering from carcinoma of the ovary, testis, and thyroid had been referred for radiotherapy following surgical excision of the primary tumour. Both cases of melanoma demonstrated metastases after surgical treatment of the primary tumour at an earlier date, the recurrences being widespread.

To provide a control series of observations, sham irradiations were also given to 34 of the 50 patients. The conditions of the sham irradiation exactly resembled those of the actual irradiation in respect of the positioning of the patient under the *x*-ray tube, the number of fields apparently irradiated, and the delineation of the fields of irradiation on the skin. The patient believed that irradiation was being carried out, and was in position under the tube for the correct period of time. The *x*-ray tube, however, was not energized.

Irradiation

Sites.—The main sites of irradiation are shown in the Table. The sacro-iliac joints and whole length of the spine were irradiated in patients suffering from ankylosing spondylitis and also in the one patient with multiple myeloma. In the patients with reticulosis, irradiation was given either to the upper half of the trunk or to the abdomen, depending upon the main sites of distribution of the lesions, the only exceptions being one individual with reticulum-cell sarcoma in whom radiation was directed to the lower part of the left half of the pelvis and upper half of the left thigh, and three

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Incidence of Symptoms After a Single Dose of X Rays to Various Sites

Radiation Given		No. of Patients		
Site	Mean Integral Dose	Irradiated	Developing Symptoms of Any Type	Developing Vomiting
Whole spine and sacro-iliac joints	4·0	21	20 (97%)	12 (57%)
Whole abdomen ..	3·4	10	9 (90%)	6 (60%)
Upper half of trunk	3·9	13	11 (84·5%)	4 (31%)
Whole body ..	2·9	4	2 (50%)	1 (25%)
Lower abdomen and thigh ..	4·2	1	0	—
Both thighs ..	3·8	1	0	—

patients to whom whole-body irradiation was given. Whole-abdominal irradiation was employed in those patients who had had testicular and ovarian tumours excised. One patient with an undifferentiated carcinoma of the thyroid was given wide-field irradiation of the upper half of the trunk; and of the two patients with melanoma metastases one was given whole-body irradiation and the other had both thighs irradiated.

Dosimetry.—All patients were irradiated with *x*-ray tubes operating at 250 kV, the tube current being 18 mA. In each instance dosage has not been expressed in terms of the number of conventional r units received on the skin or at some defined point deep to the skin, but in terms of the total amount of energy absorbed within the body, calculated in megagram-roentgens. The estimate of total energy absorption is known as the "integral" dose, and from the biological standpoint it carries greater significance than an estimate of dose in r units, allowing, with certain reservations, comparisons to be made between results obtained following irradiation in differing sites of the body. In the calculation of integral doses, valuable help has been given by Mr. J. W. Boag, of the M.R.C. Radiotherapeutic Research Unit, and the figures for whole-body irradiation have been derived from the observations of Mayneord and Clarkson (1944). The Table demonstrates the mean integral dose given in the various sites irradiated.

Results

The General Symptom Pattern

Symptoms developed in 42 out of 50 patients irradiated (84%), and the chief symptoms were found to be fatigue, anorexia, nausea, and vomiting. The pattern of symptoms in each instance was found to be very similar (Fig. 2), and

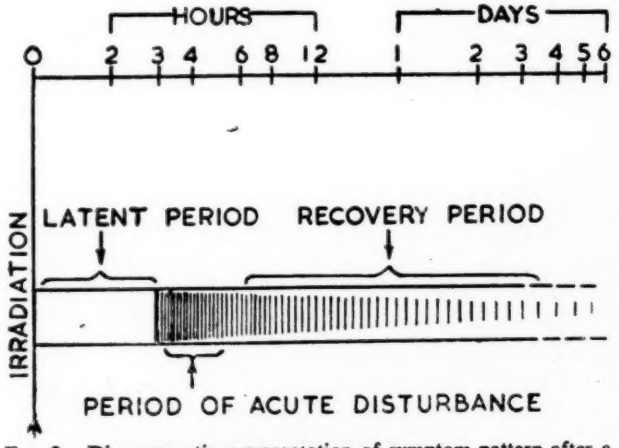

FIG. 2.—Diagrammatic representation of symptom pattern after a single therapeutic dose of *x* rays.

differed in degree only from one patient to another. The time interval which elapses from the beginning of irradiation until the disappearance of all symptoms can be divided into three main periods: the latent period, the period of acute disturbance, and the period of recovery.

Control Sham Irradiation

Information was obtained from the control sham irradiations concerning the part played by psychological and emotional disturbances in determining the incidence of symptoms. Eight out of the 34 patients developed symptoms from their sham irradiations (23.5%), but in no instance did the pattern of symptoms resemble that following the actual irradiation. It was characteristic that in these circumstances the patient complained of symptoms, chiefly headache and fatigue, either during the period of apparent irradiation or immediately after leaving the treatment room. The emotionally or psychologically disturbed patient failed to demonstrate any latent period—in complete contrast to the symptom pattern following actual irradiation. In the great majority of instances the sham irradiation was given some days before the actual irradiation, and it was noticeable that those who developed symptoms after their sham exposures did not develop any symptoms at comparable times after their actual irradiation.

Detailed Analysis of Symptom Pattern:

1. Latent Period

The mean time lapse from the beginning of irradiation to the development of symptoms was 2.7 hours. It appeared that the latent period was shorter in those patients who were generally more severely upset and who developed vomiting. A comparison made between these two groups showed that there was a difference of nearly three-quarters of an hour between the mean values of the latent periods, a difference which was found to be statistically significant (see appendix). The lengths of these two latent periods have been examined for possible influences upon them of sex distribution, dosage, disease, and site of irradiation, but no evidence has been found that these factors were responsible for the significant difference observed. It seems fair to conclude that, following a given dose of *x* rays, the more sensitive an individual is to the effects of irradiation the earlier are the symptoms likely to appear.

It will be realized that the latent period as calculated includes the period of time occupied by the positioning of the patient under the *x*-ray tube and in most instances by the irradiation of several fields. On an average this period is approximately half an hour, so that the absolute value of the latent period, assuming irradiation to have been given in an instantaneous period of time, is approximately 2.25 hours for all the patients in the series.

2. Period of Acute Disturbance

The usual complaints are of a sudden bout of nausea or of a sudden feeling of severe fatigue. Less frequent initial symptoms are headache of no particularly characteristic distribution, a feeling of dizziness or "muzziness" in the head, and an emotional disturbance taking the form of acute mental depression, in a few instances accompanied by actual weeping. Whatever the initial symptoms may be, the predominant symptoms which establish themselves in the early part of this period are fatigue, anorexia, and nausea. Objective assessment of these symptoms is practically impossible, but it appears that, after being present for a time interval varying approximately from half an hour to an hour and a half, three developments may occur, depending on the severity of the patient's upset. In the mild case the symptoms gradually subside; in the moderately severe case either the fatigue element or the feeling of nausea, or both, become accentuated for a further period of about one hour before subsiding; and in the severe case vomiting and retching supervene. Only one bout of vomiting may occur, but in the more severe cases there may be vomiting at intervals for a period of two to three hours. After the cessation of vomiting the recovery period ensues.

In studying the incidence of the various symptoms in this period of acute disturbance it is clear, both from

impressions of the observer and from the descriptions given by the patients, that fatigue appears to be dissociated from nausea and vomiting. Thus in some individuals the outstanding complaint is one of fatigue, nausea being a mild transitory symptom and vomiting not occurring at all. In rare instances the patient has never complained of nausea but solely of fatigue. On the other hand, at least four patients were encountered whose presenting symptom was nausea, which was rapidly followed by vomiting, but in whom fatigue, apart from slight tiredness apparently consequent upon the act of vomiting, did not occur at all. It was a striking observation that these latter patients remained perfectly well between their bouts of vomiting, and as soon as their vomiting ceased had no further symptoms. This suggests that two aetiological disorders may underlie the development of these symptoms—one associated with fatigue and the other with nausea and vomiting.

A detailed analysis of the incidence of symptoms for each site irradiated, and in particular for the incidence of vomiting, is shown in the Table. The incidence of vomiting when irradiation was confined to the upper half of the trunk was 31%, as opposed to an incidence of 60% when the abdomen alone was irradiated. However, the total numbers in each group are small, and, by considering all instances in which radiation was not directed to the abdomen in contrast to all those in which the abdomen was irradiated, irrespective of whether radiation was directed to other sites as well, the relevant figures are 29% and 53%. Statistically these two sets of figures are not significant, but in the larger group the difference approaches much nearer to a significant level than in the smaller group. It is possible that with an even larger series of patients a significant difference may be found in the incidence of vomiting, depending on whether the abdomen is irradiated or not.

During this period of acute disturbance no consistent changes have been noted in the pulse rate, blood pressure, body temperature, and respiration rate up to the act of vomiting.

3. Recovery Period

An accurate estimation of the recovery period is difficult, but it is possible to make an approximate estimate to the nearest day. With the subsidence of the period of acute disturbance the patient is left with a feeling of mild fatigue, nausea, and anorexia. Depending on the degree of acute disturbance, these symptoms either persist for one day or less, or extend in the most severe instances over a period of up to five days. In the most severely upset patients nausea may persist for two to three days, but of the three outstanding symptoms it is the first to disappear. Its disappearance is followed by the gradual subsidence of fatigue and anorexia, in that order.

The General Radiation Syndrome

The pattern of symptoms following a single dose of *x* rays within therapeutic limits having been demonstrated, the basic pattern of the general radiation syndrome, observed after the exposure of both animals and man to high levels of radiation, must now be considered.

The main features of the general radiation syndrome are depicted in Fig. 1. This diagram was derived from the observations made upon Japanese necropsy material and from the histories and clinical features of the survivors (Liebow, Warren, and De Coursey, 1949). It will be seen that there are four main periods in which clinical disturbances and death may or do occur, which may be designated: the period of initial reaction, the period of acute reaction, the period of subacute reaction, and the period of chronic reaction.

Period of Initial Reaction.—This supervenes after a brief latent period following exposure, and is characterized by nausea, vomiting, and fatigue. It is probable that the mean length of this latent period is approximately two hours, although species differences and the level of dosage received may well determine its actual length. In the Japanese cases the latent period is said to have been in some instances as short as half an hour. On the other hand, Painter and Brues (1949) state that the initial signs and symptoms occur within the first six hours in man, the dog, rat, mouse, guinea-pig, and goat. Theoretically it is possible for a human being to die during this stage, as it has been shown that animals subjected to radiation of very high intensity may die either during the period of irradiation or within a few hours of its cessation (Henshaw, 1944). It is generally stated that in most instances the duration of the initial reaction is approximately two to three days and that following its disappearance a period of comparative well-being ensues before the next stage of the general radiation syndrome supervenes. It appears likely, however, that in some of the Japanese casualties and also in some rats and dogs (Painter and Brues, 1949) this period of initial reaction is prolonged towards the end of the first week after exposure, and terminates in death. The human beings showing this developed high fever, thirst, diarrhoea, and delirium before they died. At the time of death clinical evidence of bone-marrow damage was not prominent, and it seems likely that death at this stage is the outcome of an extremely severe form of damage inflicted during the original irradiation.

Period of Acute Reaction.—This stage becomes apparent towards the end of the second week, and is characterized by the clinical features of acute marrow failure, of ulceration of the mucous membrane of the gastro-intestinal tract, of acute secondary infections, and also by epilation.

Period of Subacute Reaction.—This stage occurs at about the end of the sixth week, at which time the marrow damage, clinically obvious in the preceding phase, is becoming less marked. At this stage death may result from lung or brain abscess, persistent ulceration of the large bowel, an exacerbation of a pre-existing focus of infection, and malnutrition.

Period of Chronic Reaction.—The preceding period of subacute reaction probably merges insensibly into the period of chronic reaction, where the presenting features and causes of death are malnutrition, chronic anaemia, chronic infections, premature senility, and possibly leukaemia.

It will be realized that in the majority of patients the complete syndrome will not be shown. In these patients, depending on the amount of radiation received during the original exposure and the inherent radiosensitivity of the individual, one or more of the acute manifestations may develop, resulting in some instances in death. On the other hand, there may only be evidence of mild upset, probably in the form of a minor degree of suppression of marrow function and some epilation. Finally, a proportion of individuals will show no clinical features of the syndrome, but haematological investigation will demonstrate an abnormally low total white-cell count.

Conclusion

It has been shown that, following a single dose of *x* rays within therapeutic limits and of the order of 3–4 megagram-roentgens, there is a well-defined latent period which terminates in the sudden onset of symptoms, and that the period of acute disturbance, after lasting for a variable number of hours, passes into a recovery phase. The total duration of the symptomatic disturbances has been shown to vary from one to five days, depending on the radiosensitivity of the individual and the actual dose given. The similarity of the symptom pattern following the therapeutic dose of *x* rays to the period of initial reaction, the first manifestation of the general radiation syndrome, is evident. The close agreement in the length of the latent periods and the similarity of the symptoms justifies the conclusion that after therapeutic *x*-ray doses the symptom pattern is a milder version of the symptom pattern of the period of initial reaction seen in animals after mid-lethal doses. This conclusion indicates that it is justifiable to utilize observations made

after a single therapeutic dose of *x* rays in the interpretation of the consequences of exposure to irradiation of greater and possibly lethal proportions.

Summary

The pattern of symptoms following a single therapeutic dose of *x* rays has been described, based on the findings in a group of 50 patients. The pattern was found to consist of three well-defined phases : a latent period extending from the administration of the *x* rays to the onset of symptoms ; a period of acute disturbance which persisted for approximately between one and a half and four hours after the onset of symptoms, depending on the degree of upset ; and a recovery period which in the most acutely disturbed patients extended over four to five days. In those patients in whom the period of acute disturbance was not associated with vomiting the latent period was found to be significantly longer than in those who vomited.

A brief description has been given of the general radiation syndrome produced in man and in many types of mammals following a single mid-lethal dose of *x* rays, in which four general periods of reaction can be discerned : the periods of initial reaction, acute reaction, subacute reaction, and chronic reaction.

The similarity between the pattern of symptoms following therapeutic doses of *x* rays and the symptoms of the period of initial reaction of the general radiation syndrome has been stressed, and attention has been drawn to the possible value of using clinical studies based on single therapeutic doses of *x* rays to interpret what may occur when, either accidentally or under conditions of war, much higher doses are received.

No account has been given of the physiological disturbances produced by therapeutic doses of *x* rays, which will form the subject of a later communication.

I wish to thank Professor J. McMichael and Dr. Russell Fraser, of the Department of Medicine, Dr. J. F. Loutit, of the M.R.C. Radiobiological Research Unit, A.E.R.E., and Dr. C. A. P. Wood, Director of the M.R.C. Radiotherapeutic Research Unit, for their advice and criticism.

APPENDIX

The mean length of the latent period in the less severely upset group of patients (Group A) has been compared with that in the more severely upset group (Group B). The distribution of the different lengths of the latent periods within each group, the value of the mean and t and P values of the difference of the means are shown below.

	Length of Latent Period (Hours)							
	1–1·49	1·50–1·99	2·0–2·49	2·5–2·99	3·0–3·49	3·5–3·99	4·0–4·49	4·5–4·99
Group A (19 patients) ..	0	1	2	7	0	7	2	0
Group B (23 patients) ..	5	4	4	4	1	2	1	2

Mean length of Group A = 3.06 hours } Difference of mean
Mean length of Group B = 2.44 hours } lengths = 0.62 hr.
The t value of the difference is 2.10, indicating that $P<0.05$ and that the difference is significant.

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ORAL N,N'-DIBENZYLETHYLENE-DIAMINE PENICILLIN IN CHILDREN

BY

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The greatest drawback to the use of oral penicillin has been, in our experience, the variability with which it is absorbed into the blood stream. Several penicillin derivatives have been tried in different dosages, with and without antacids, before and after meals, and scaling the dosage according to body weight. While in a good proportion of cases therapeutic blood levels have been obtained by the oral route, with no preparation have consistent levels been observed; this has meant that, when any case has been treated with oral penicillin, blood-level estimations have been essential to confirm that the antibiotic was being absorbed.

Recently a new salt N,N'-dibenzylethylenediamine penicillin has been available (Szabo, Edwards, and Bruce, 1951) ; this is referred to here as " penidural." It has been the subject of a recent report by Fletcher and Knappett (1953) as a long-acting repository penicillin following intramuscular injection ; we have investigated it from the point of view of reliability of absorption following oral administration.

Side-effects.—Several adults have complained of borborygmi and urgency at stool during the first 24 hours of treatment but not subsequently. No children of any age have been disturbed, and the palatability of the product has made its administration easy.

Material and Methods

Penicillin blood levels were estimated, using a dilution technique with a strain of *Staphylococcus aureus* of sensitivity to 0.03 μg. of penicillin per ml. A total of 101 children of all ages were given 300,000 units of penidural and their blood levels were estimated three to four hours after administration for reliability of absorption. In addition a small series of 17 adult volunteers were investigated with the same preparation.

The penidural was given irrespective of the times of meals and whether the stomach might be full or not.

Results

Fig. 1 shows that the antibiotic was reliably absorbed in all of the 118 cases in which it was administered, and Table I shows the levels obtained in the 101 children. In several

TABLE I.—*Serum Penicillin Levels in 101 Children Three Hours After 300,000 Units of Penidural*

Weight in lb.	0·06 unit per ml.	0·125 unit per ml.	0·25 unit per ml.	0·5 unit per ml.	Total Cases
0–10	—	1	4	—	5
11–20	—	5	2	1	8
21–30	7	4	6	1	18
31–40	10	13	—	2	25
41–50	8	8	1	—	17
51–60	5	7	—	—	12
61–70	5	5	1	—	11
71 and over	1	4	—	—	5
TOTALS	36	47	14	4	101

TABLE II.—*Serum Penicillin Levels in Units per ml. at 3 p.m. on Consecutive Days. 300,000 Units of Penidural Given Six-hourly Throughout*

Case No.	3 hours	27 hours	51 hours	75 hours
1	0·06	0·25	0·25	0·25
2	0·125	0·25	0·25	0·25
3	0·25	0·5	1·0	1·0
4	0·125	0·5	0·5	0·5

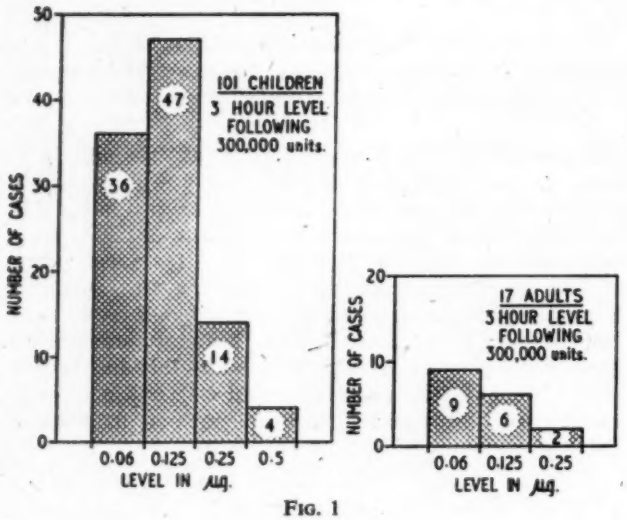

FIG. 1

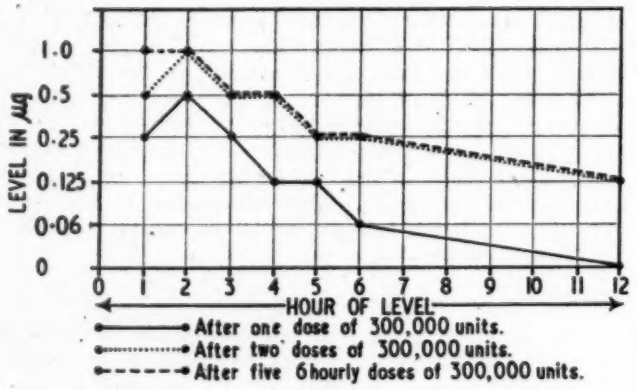

FIG. 2

cases hourly penicillin levels were estimated and a cumulative effect was seen following a second oral dose. Fig. 2 shows one such typical example, in which there were satisfactory blood levels for six hours, but no residual level at 12 hours after a single dose. When a second dose was given at six hours, not only were the levels for the succeeding six hours higher than in the first period but there was also a residual level at 12 hours.

In Table II are shown the blood levels at 24-hour intervals in four consecutive patients of differing weights and ages to whom six-hourly penidural was being given. Blood samples were taken at the same time each afternoon, three hours after the last dose of the drug. Each shows the same increase in blood levels as is depicted in Fig. 2. There was some indication in the figures shown in Table I that better blood levels were obtained when penidural was given before meals.

Discussion

Penidural is the first oral preparation of penicillin which has in our experience been reliably absorbed in 100% of patients, irrespective of size and weight and using a standard dosage of 300.000 units. No attempt has been made to work out a graded system of dosage according to body weight, but it is possible that in the smaller children therapeutic blood levels might be obtained with lesser amounts of penidural. The emergence of a reliable oral penicillin seems to bring this drug into line with the newer antibiotics where penicillin-sensitive organisms are being dealt with.

In the treatment of acute infections blood levels during the first six hours with this oral penicillin alone cannot be regarded as adequate, and in five cases of acute illness in which penidural has been used therapeutically a single intramuscular injection of a large amount of crystalline penicillin has been used to augment the blood level during this period. In these cases—two of osteomyelitis and three of pneumonia—the results obtained have been as good as those which would have been anticipated had intramuscular penicillin been chosen for treatment.

A rational scheme of treatment of acute infection appears to be an initial intramuscular injection of 600,000 units of penidural (Fletcher and Knappett, 1953) and 100,000 units of crystalline penicillin, with 300,000 units of penidural orally, the treatment continuing thereafter only with oral penidural. Such a scheme will produce reliable therapeutic penicillin levels and should be adequate to treat infection by penicillin-susceptible organisms. Abuse of this new penicillin preparation is likely to enhance the growing number of strains of penicillin-resistant bacteria, and it is hoped that the growing menace of penicillin-resistant staphylococci will not be unnecessarily increased by improper dosage or dose-spacing.

We are indebted to Messrs. John Wyeth, Ltd., London, for a plentiful supply of penidural.

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COMBINED ORAL PENICILLIN AND SULPHADIMIDINE IN ACUTE MIDDLE-EAR INFECTIONS

BY

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Modern antibacterial drugs have revolutionized the treatment of acute otitis media, and the role of surgery in this condition is of rapidly diminishing importance. Before the discovery of antibiotics, sulphonamide administration was an established part of the therapy of this condition (Hall, 1948). Owing to the limitations imposed by toxicity upon the attainable blood sulphonamide level, and the diversity of the invading organisms, it is not surprising that sulphonamides alone are often unable to quell the infection.

The Literature

The commonest causal agents are *Staph. aureus* and *Str. haemolyticus*; consequently much better results follow the use of penicillin as the antibacterial agent (György *et al.*, 1946; Lierle and Paul, 1946; Robinson *et al.*, 1948; Jersild and Kiørboe, 1950). However, this still leaves the dangerous residue of insensitive Gram-negative bacilli, notably *Bact. coli* and *Proteus* strains, which are often present in varying numbers in a mixed infection. Elimination of the main infecting bacteria allows, and even stimulates, these fellow-travellers to multiply rapidly and restore the severity of the original disease condition.

Of the newer antibiotics, streptomycin carries with it a danger of vestibular damage and is unlikely to commend itself for the treatment of infections in the aural cavities. Chloramphenicol and aureomycin, with a wider antibacterial range, approach more closely to being ideal drugs for the

treatment of this condition. The cost of these antibiotics, however, is prohibitive; and, if used with penicillin, the superior bactericidal power of the latter might be prejudiced by their antagonistic action (Armstrong and Larner, 1951). My personal impression of a very limited trial of chloramphenicol is that it is not quite so effective in a mixed infection as penicillin and a sulphonamide combined.

That such a combination results in a pronounced synergism between the two drugs has been repeatedly demonstrated in the laboratory (Bigger, 1944; Chain and Duthie, 1945; Kolmer, 1948). Further, this synergistic action extends to Gram-negative organisms such as *Bact. coli* and *Bact. typhosum* (Stewart, 1947; Thomas and Hayes, 1947; Bigger, 1950; El Borolossy and Buttle, 1950). The action of the sulphonamides in preventing destruction of penicillin by penicillinase (Cronheim and King, 1951) may be of importance when dealing with these latter organisms. On the clinical side there are very few reports of combined therapy with the two drugs, although Johnson *et al.* (1951) have described a synergistic action between oral penicillin, sulphadiazine, and sulphamerazine in the treatment of gonorrhoea. On the other hand, Nielsen and Søttrup (1951) found no difference between combined therapy and therapy with either drug alone in the treatment of pneumonia. I can trace no records of similar treatment in acute otitis media, although Moffett and Dalton (1949) have successfully treated acute mastoiditis with penicillin and sulphadiazine. It is the purpose of this paper to describe a number of cases treated with sulphadimidine and penicillin, with particular emphasis on the oral route for the latter drug.

There can be no doubt that, when administered on an empty stomach, penicillin is well absorbed from the first part of the duodenum in a dosage some five times in excess of that by injection (Little and Lumb, 1945; Buchanan, 1946; Husson, 1947; Markowitz and Kuttner, 1947; Reisman *et al.*, 1947; Stewart and May, 1947; Cohlan *et al.*, 1948). Hypochlorhydria, occurring as a result of severe illness, contributes to this (Buchanan, 1946; Anderson and Landsman, 1947; Bicknell, 1951). The adequate clinical effect of oral therapy in serious illnesses such as pneumonia has been amply demonstrated (Bunn *et al.*, 1945; Finland *et al.*, 1945; Suchett-Kaye and Latter, 1947; Anderson and Landsman, 1947; Eadie *et al.*, 1951). Good results have also been claimed in ear, nose, and throat infections (Robinson *et al.*, 1948; Wheatley, 1951). Oral administration is of greater convenience in general practice, where most cases of acute otitis media are likely to be seen. As this infection most commonly occurs in children, the oral route is again particularly desirable. For combination with sulphonamides, too, it is convenient to administer both drugs together by mouth, at the same dosage intervals. After some trial I adopted an eight-hourly interval for the treatment of these cases. This is a schedule which others have found to be highly effective with oral penicillin in pneumonia and scarlet fever (Bunn *et al.*, 1950; Weinstein and Perrin, 1950). Bunn and his co-workers also treated some of their cases with 12-hourly dosage, as did Austrian *et al.* (1951). Results were comparable with those following parenteral therapy.

In treating the acute middle-ear infection, the ideal procedure is to institute chemotherapy before perforation of the tympanic membrane can occur; thereby spontaneous perforation or the need for paracentesis may be avoided. The latter procedure is a difficult one to perform in general practice, and I am not convinced of its absolute necessity. Simpson (Fleming, 1950), considering this question in relation to penicillin therapy, advises paracentesis after 24 hours if there is no improvement. He rightly stresses that the object of treatment is the preservation of the function of hearing, and points out that even a sterile collection of fluid in the middle-ear may lead to resultant adhesions, and possible recurrence later. I personally feel that such a collection of fluid will naturally drain away via the Eustachian tube, without the need for paracentesis. However, in order to prevent the possibility of serious permanent disability chemotherapy must be prompt and adequate.

Results

The cases have been divided into two groups, classified as mild and severe. Mild cases were those in which there was little constitutional disturbance but inflammation and bulging of the tympanic membrane were present. Severe cases were those in which there was much pyrexia and pain, or in which perforation of the ear-drum had already occurred before they were seen. Most of the mild cases were treated with penicillin alone, sulphadimidine being held in reserve in case there was not a prompt response to treatment. The severe cases were treated mainly with combined penicillin and sulphadimidine from the onset. Chloramphenicol was substituted in three cases when the results of bacteriological examination showed an organism highly sensitive to this antibiotic. In these cases the response to combined therapy had not been as immediate as in the other cases in the series. The results are tabulated and compared with some earlier results obtained with sulphonamides alone and with parenteral penicillin. These cases do not include acute exacerbations occurring in chronic otitis media. The standard dose for adults was 0.375 g. (600,000 units) of penicillin plus 1 g. of sulphadimidine, eight-hourly by mouth; there was a proportionate reduction in amounts for children.

Comparison of Results

Treatment	Cases			Perforated Before Treatment	Perforated After Treatment	Recurrence in 3 Months	Chloramphenicol Substituted
	Mild	Severe	Total				
S.	3	4	7	3	Nil	3	Nil
Inj. P.	8	9	17	8	2	1	,,
Inj. P. and S.	3	5	8	3	Nil	1	,,
Oral P.	23	6	29	6	,,	Nil	1
Oral P. and S.	4	28	32	13	,,	1	2
Total	41	52	93*	33	2	6	3

S. = Sulphonamide. P. = Penicillin. * There were 2 separate attacks in 4 cases.

Bacteriology.—Swabs were taken from one-third of the 33 cases in which perforation had occurred before treatment was begun. The cultures gave the following results:

Staph aureus	3 cases
,, ,, and diphtheroids	1 case
,, ,, ,, *Proteus*	1 ,,
,, ,, ,, *Bact. coli*	1 ,,
Bact. coli, pneumococci, and *Staph. albus*	1 ,,
Staph albus (48 hours after treatment)	1 ,,
β Str haemolyticus	1 ,,
β ,, ,, *Staph. albus*, and diphtheroids	1 ,,
Sterile	1 ,,

Late Results.—General practice offers some unique opportunities for follow-up of these cases, with particular reference to late effect on hearing. This is so because over the course of years many of these patients are seen from time to time for other ailments. About three-quarters of the cases described here have been thus observed for periods of one to three years. In none of these was there any residual hearing defect, as measured by their ability to hear the whispered voice at 15 feet (4.6 metres) with the affected ear alone. Where perforation had occurred healing took place in every instance. Sometimes a minute scar could be seen at the site of the perforation; but in many it was impossible to detect any evidence of the previous rupture of the membrane or of the original infection. The six cases in which there was a recurrence in three months resolved with further treatment. In four cases there were repeated but separate infections (often in the opposite ear). These also resolved with repeated treatment, and further attacks were prevented when infected tonsils and adenoids were removed.

Conclusions

The small numbers of cases treated with sulphonamides alone and with parenteral penicillin offer no basis for accurate comparison. However, they are useful in that they indicate that oral penicillin is no less effective than penicillin by injection. Of the seven cases treated with sulphonamides

alone there was a recurrence within three months in three. This was regarded as an unsatisfactory result. Although one case out of 32 treated with oral penicillin and sulphadimidine suffered a recurrence in three months, it must be borne in mind that this group included by far the greatest number of severe cases. The satisfactory end-results in 93 cases of acute otitis media treated with chemotherapy alone are held to obviate the necessity for surgical intervention. The results of bacteriological examination in 11 cases indicate that the majority of cases are probably due to infection with penicillin-sensitive organisms, but that non-sensitive bacteria, particularly *Bact. coli*, form an important minority. It is held that the co-administration of sulphonamides with penicillin will effectively deal with most of these infections. This is particularly important in those cases (the majority) in which perforation of the ear-drum has not occurred and, as a result, the nature of the invading micro-organism cannot be ascertained. In the occasional instance in which a more specific antibiotic is required, combined therapy will stay the infection until the result of bacteriological examination is known.

Summary

The role of chemotherapy in acute otitis media is discussed and the advantages of combining penicillin and a sulphonamide are outlined. The synergistic action of these two drugs and the desirability of co-administration in mixed infections is stressed. The literature on oral penicillin administration is surveyed, and it is concluded that this is an effective and convenient method of administering the antibiotic.

The results in 93 cases of acute middle-ear infection are described. Of these, 61 were treated with either oral penicillin alone or oral penicillin and sulphadimidine, according to severity. Out of 34 severe cases treated in this manner, perforation of the tympanic membrane had already occurred in 19 before treatment was begun. The results were uniformly good, with no permanent sequelae or after-impairment of hearing. Healing of the ear-drum occurred in all cases in which perforation had occurred. The bacteriology in 11 cases showed a preponderance of infection with *Staph. aureus* and *Str. haemolyticus*. However, the infection was usually a mixed one, with *Bact. coli* and *Proteus* as the usual co-invaders.

I wish to express my thanks to Dr. L. W. Cann, of Ashford County Hospital, for undertaking the bacteriological examinations.

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THE Q-T INTERVAL IN MYOCARDIAL INFARCTION

BY

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The Q–T interval of the electrocardiogram is measured from the beginning of the Q wave to the point where the T wave ends at the isoelectric line. It is an indication of the total time occupied by ventricular excitation and recovery. Recently, great interest has been evinced in this hitherto neglected feature of the electrocardiogram, and its variations have been reported in a variety of conditions.

A statement in a leading textbook of electrocardiology (Wolff, 1950) that "abnormal Q–T occurs regularly as a result of myocardial injury. If QRS is normal, the prolonged Q–T must signify a profound disturbance in the recovery process" aroused interest in this question, and, as a search of the literature of the subject was barren in its results, this particular study was embarked on.

Clinical Material and Methods

As this study was undertaken to evaluate the significance of the Q–T interval in myocardial infarction particularly, it was decided to rule out all possible variables. For this purpose all the normals which serve as controls were selected from the ages of 40 and above. It was also made absolutely certain that all the normals had no electrocardiographic abnormality. The group of cases of myocardial infarction selected was also carefully scrutinized to exclude any which showed any changes of rhythm, of ventricular hypertrophy, of bundle-branch block, or of hypertensive heart disease, or which demonstrated either erect or inverted U waves. Also, any patient who had had digitalis (Berliner, 1931) or who had been on a regime of mercurial diuretics was discarded.

A total of 600 normal tracings (400 males and 200 females) and 800 tracings of myocardial infarction were studied. All the tracings had been taken on the standard Cambridge string-galvanometer electrocardiogram, by the same individual, with the same standardization (1 mV=1 cm.). In the examination of each tracing a strict routine was adhered to, the tracings being examined under a powerful magnifying-glass. Any tracing which showed any abnormality in the shape or the duration of the QRS complex was discarded, as were also all tracings in which the end of the T wave was not clearly definable. Each Q–T interval was measured from the point at which the Q wave (in the absence of the Q wave, the R wave) left the isoelectric line to the point where the T wave after its excursion returned to the isoelectric line. Each R–R interval was measured from the peak of the R wave of one complex to the peak of the R wave of the next complex.

To calculate the Q–T and R–R intervals the following procedures were followed: (1) Any two Q–T and R–R intervals were measured in each of Leads II, aVF, V_2, and V_4, giving a total of eight separate values for both the Q–T and the R–R intervals. (2) The Q–T_c—Q–T interval corrected to the rate (Taran and Szilagyi, 1947) of each corresponding Q–T and R–R interval—was worked out as explained below. (3) The average of these eight Q–T_c's was taken as the final Q–T_c figure. This procedure was followed in each tracing throughout the 1,400 tracings studied.

Methods of Calculation of Q–T_c

Various formulae have been recommended from time to time for the correlation of the Q–T interval to the cardiac cycle. The one that is simplest and has stood the test in most studies on the Q–T interval is that formulated by Bazett (1920):

$S = K\sqrt{C}$, where S = systole = (Q–T)
C = cycle-length = (R–R)
K = 0.37 second for males and 0.40 second for females

Taran and Szilagyi (1947) introduced a very important new conception—the Q–T_c—namely, the duration of the Q–T interval corrected for the cycle-length. By the use of this modification, Bazett's formula standardizes the Q–T interval to a heart rate of 60 a minute, or, in other words, to a cycle-length (R–R interval) of 1 second. Now, the formula can be expressed as:

$$Q\text{–}T_c = \frac{Q\text{–}T}{\sqrt{R\text{–}R}}$$

To obviate tedious calculations involved by this formula, use was made of the slide-rule method (Fox *et al.*, 1950), based on Taran and Szilagyi's modification of Bazett's formula. After the first few calculations on the slide-rule, Kissin's nomogram (Kissin *et al.*, 1948) was used in conjunction with the slide-rule. This nomogram is based on Taran and Szilagyi's modification of Bazett's formula, and employs exactly the same principle as the slide-rule method. Since no differences were recorded in the use of either of these methods, after the first 200 readings, Kissin's nomogram was employed in all cases.

All figures obtained were statistically analysed by the formula $\sigma = \sqrt{\frac{\Sigma(x-\bar{x})^2}{n}}$ and found to be admissible.

Results

The results of the normal electrocardiographic tracings of the 400 males and 200 females, divided into age groups, are shown in Table I. In both the normal males and females there seems to be an inverse relationship between age and the duration of Q–T_c, but when the χ^2 test was applied no significant difference was found. Sex, however, definitely seems to play a part, the average Q–T_c for normal males being 0.394 second, with a range of 0.387 to 0.401 second; and the average for females 0.406 second, with a range of 0.399 to 0.413 second.

TABLE I.—*Q–T_c Plotted Against Age for Normal Males and Females (Aged 40 and Over)*

Age Group	No. of Cases		Mean Q–T_c in Seconds		Q–T_c Range in Seconds	
	Male	Female	Male	Female	Male	Female
40–49 ..	124	97	0·398	0·415	0·392–0·404	0·409–0·421
50–59 ..	163	54	0·397	0·404	0·392–0·402	0·399–0·409
60+ ..	113	49	0·388	0·400	0·379–0·397	0·391–0·409
Total ..	400	200	0·394	0·406	0·387–0·401	0·399–0·413

TABLE II.—*Comparison of Q–T_c in Seconds in Normal Subjects Obtained by Various Authors*

Author	Males	Females	Average Q–T_c
(1) Bazett (1920)	0·370	0·400	0·385
(2) Dock (1931)	0·3841	0·3890	0·3885
(3) Cheer (1930)	0·3743	0·3877	0·3810
(4) Taran and Szilagyi (1947)	—	—	0·3924
(5) Alimurung *et al.* (1950)	0·403	0·400	0·4015
(6) Krasnoff (1950) ..	0·392	0·406	0·399
(7) Present study	0·394	0·406	0·400

In studies (1), (2), (3), and (5) "K" is used instead of "Q–T_c."

These "control" readings are compared with those obtained by other authors (Table II). It will be noticed that almost all the figures approximate one another closely. Moreover, if it is appreciated that the studies of Taran and Szilagyi and of Alimurung *et al.* contained only children, further proof is added to the statistical contention already stated that Q–T_c has no correlation with age.

Q–T_c in Cases of Myocardial Infarction

Eight hundred electrocardiographic tracings following myocardial infarction were studied (496 of males, 304 of females). The procedure used in measuring the Q–T_c was exactly as already outlined. The Q–T_c's in males and females were plotted against the localization of the infarct, and this is shown at various stages of the infarcts—on the first day, at the end of the first week, at the end of the first month, at the end of the sixth month, at the end of a year, and at varying periods after a year. Tables III and IV demonstrate the changes taking place in males and females respectively.

TABLE III.—*Average Q–T_c at Various Periods After Myocardial Infarction in Males, Plotted Against Localization of Infarct*

Localization of Infarct	No.	Average Q–T_c in Seconds					
		1st Day	1st Week	1st Month	6th Month	1st Year	1 Year+
Antero-lateral	238	0·425 (39)	0·485 (35)	0·475 (60)	0·460 (64)	0·443 (13)	0·413 (27)
Posterior	192	0·430 (32)	0·430 (36)	0·417 (52)	0·416 (33)	0·443 (20)	0·413 (19)
Antero-septal	66	0·431 (19)	0·427 (16)	0·415 (20)	0·411 (11)	—	—

The figures in parentheses show the total number of tracings in each group.

TABLE IV.—*Average Q–T_c at Various Periods After Myocardial Infarction in Females, Plotted Against Localization of Infarct*

Localization of Infarct	No.	Average Q–T_c in Seconds					
		1st Day	1st Week	1st Month	6th Month	1st Year	1 Year+
Antero-lateral	112	0·414 (30)	0·460 (34)	0·434 (35)	0·430 (6)	0·421 (7)	—
Posterior	108	0·470 (32)	0·465 (32)	0·450 (24)	0·435 (9)	0·418 (11)	—
Antero-septal	84	0·474 (17)	0·466 (21)	0·431 (25)	0·424 (8)	0·414 (13)	—

The figures in parentheses show the total number of tracings in each group.

It will be noticed that exactly the same pattern is followed in both the sexes. In antero-lateral infarctions, after a preliminary rise of the Q–T_c interval on the first day, there is a further maximal rise at the end of the first week, after which it gradually regresses, but fails to reach normal levels. In the posterior and antero-septal infarctions the maximal rise is seen on the first day, and then the Q–T_c interval regresses, until after a year it is nearing normal limits. Hence it is evident that the localization of the infarct has no direct bearing on the Q–T_c, this particular interval being always prolonged in the acute stages and gradually tending to return to normality with the healing of the infarct.

TABLE V.—*Average Q–T_c in Males and Females at Various Periods After Infarction*

Period of Time Elapsed After Infarction	Average Q–T_c in Seconds			
	Males		Females	
	No.	Q–T_c	No.	Q–T_c
1 day	90	0·425	79	0·423
1 week	87	0·458	87	0·482
1 month	132	0·450	84	0·470
6 months	108	0·440	23	0·454
1 year	33	0·424	31	0·423
1 year+	46	0·414	—	—

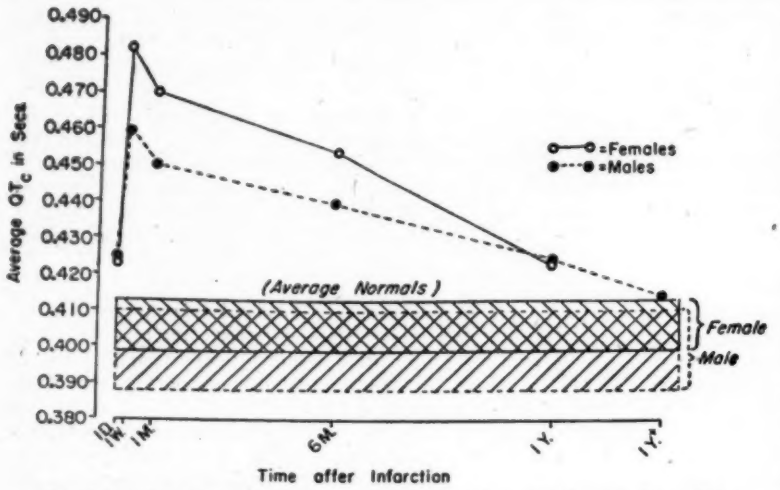

Chart showing average Q–T_c in males and females at various periods after infarction.

Since the localization of the infarct does not play a significant part, but the stage of the infarct does, it was decided to tabulate the Q–T_c's against the period of time elapsed after infarction, irrespective of the localization. This is shown in Table V and the Chart.

Discussion

The Q–T interval of the electrocardiogram represents the period of electrical systole of the heart. Katz (1921) suggested that measuring the duration of systole in diseased hearts compared with normal hearts would give a method of determining the functional integrity of the myocardium. White and Mudd (1929) pointed out that the Q–T interval is prolonged in paroxysmal tachycardia or disorders causing a marked widening of the QRS complex, but not in conditions associated with structural defects. Dock (1931) did not regard the Q–T interval as a satisfactory index of cardiac function, since only one-third of patients with failing hearts have electrical systoles longer than the maximum in normal subjects of the same sex and age. Moreover, he found that the duration of the Q–T interval in hypertensives with left ventricular enlargement without failure is the same as in those who are badly decompensated.

In 1939 Ashman disagreed with the above authors, and showed that measurement of the electrical systole gives valuable information regarding the degree to which the myocardium is affected in cases of diphtheria or acute rheumatic carditis. Taran and Szilagyi (1947) confirmed this in cases of acute rheumatic carditis, though their results are vigorously contested (Alimurung *et al.*, 1950). Similar prolongation of the Q–T interval has been noted in cases of hypopotassaemia (Bellet and Dyer, 1937; Stewart *et al.*, 1940; Brown *et al.*, 1944; Currens and Crawford, 1950); and in cases of hypocalcaemia (Carter and Andrus, 1922; Kellogg and Kerr, 1936; Barker *et al.*, 1937).

Katz (1921), Robb and Turman (1947), and Horwitz and Graybiel (1948) have shown that many physiological factors such as cellular metabolism, sex, and position may influence the Q–T interval. Berliner (1931), Bayley (1942), Savilahti (1945), and Krasnoff (1950) have shown that prolongation of the Q–T interval occurs in hypertension, bundle-branch block, ventricular hypertrophy, etc. (pathological cardiac states). Hence it may be taken as fairly certain that ischaemia and injury of the myocardium have a bearing on the duration of the Q–T interval.

As all these various factors may be playing a part, it is difficult to estimate the effects of one or many of these possible factors on the prolongation of the Q–T interval. However, this study definitely supports previous work of Krasnoff (1950) that the Q–T interval is prolonged in the early stages of myocardial infarction, and gradually diminishes until, after about one year, average normal levels are approached. There are good grounds for believing that the prolongation of the Q–T interval is directly related to the myocardial damage, though the immediate mechanism remains unknown. A good correlation exists between these results and the findings of Mallory *et al.* (1939), which demonstrated the changes in the cardiac musculature following acute myocardial infarction. These results are summarized in Table VI. It will be seen that necrosis of the musculature starts on the first day, and reaches a maximum at one week, when there is maximum dead and dying muscle. At the end of a month granulation tissue is present, and clearance of the dead muscle is being effected, and collagen has started to be laid down—the earliest signs of repair. At the end of six months repair is fairly well advanced, and at the end of a year there is maximum deposition of collagen.

The Chart shows that the changes in the Q–T_c interval closely follow this pattern. Thus the Q–T_c interval increases on the first day, reaches its maximum at the end of a week, when cardiac damage is at a maximum, and then gradually recedes as the process of repair sets in.

Hence the Q–T_c interval may prove to be of use in estimating the duration of rest in bed, so that activity is indulged in only when a firm process of repair has set in.

Summary

The Q–T interval is dependent on the cardiac rate. The average normal Q–T_c was found to be 0.394 second, with a range of 0.387–0.401 second for males, and 0.406 second, with a range of 0.399–0.413 second for females. The Q–T interval has no relation to age. It was found to be prolonged in cases of acute myocardial infarction reaching a maximum at the end of the week, gradually approaching normal limits again after about one year. A definite correlation is shown between the length of the Q–T_c and pathological changes in cardiac musculature of cases of acute myocardial infarction. The Q–T_c bears no relation to the localization of the infarct.

The methods of selection of cases, the choice of the formula used, and the methods of measurement are described in detail.

TABLE VI.—*Pathological Changes in Cardiac Muscle Following Myocardial Infarction in Relation to Time-interval (Modified from Mallory et al., 1939)*

Time Interval	Necrotic Muscle	Polymorphs	Blood Vessels and Connective Tissue	Removal of Fibres	Pigmented Macrophages	Eosinophils	Plasma Cells and Lymph	Collagen
1 day	++	+	0	0	0	0	0	0
1 week	++++	+++	++	+	+	+	+	0
1 month	+	0	++++	++	++++	0	++++	++
6 months	0	0	++++	?	+	0	+	+++
1 year+	0	0	++++	0	+	0	0	++++

The relation of the Q–T interval to various physical, chemical, and pathological states is discussed.

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CHLOROQUINE IN THE TREATMENT OF AMOEBIC LIVER ABSCESS

BY

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The antimalarial action of the derivatives of the 4-aminoquinoline series was thoroughly established during the last war, and from among the series chloroquine (7 - chloro-4(4-diethylamino-1-methylbutylamino)-quinoline diphosphate) was found to be one of the most effective compounds, and to be of low toxicity. Observations revealed that the drug had a peculiar depot action, being stored in the liver in concentrations as high as 500 to 600 times the plasma level (Conan, 1948). This property of the drug, as well as its pronounced antiplasmodial activity, led to the testing of its possible efficacy in protozoan infections other than those caused by malaria plasmodia. Tests carried out in England and America immediately after the war showed that it had a pronounced action in *Entamoeba histolytica* infections of the liver that were responsible for hepatic amoebiasis and liver abscesses. These experimental findings now seem to be generally confirmed by clinical trials.

Conan (1949) used chloroquine successfully in seven cases of amoebic hepatitis and found that it was an effective chemotherapeutic agent for the treatment of amoebic infections of the liver, being at least as effective as emetine but apparently without the latter's toxicity. In the same year Manson-Bahr (1949) reported his experience with chloroquine in a case of *E. histolytica* liver abscess in a very advanced stage, which could not be influenced either by emetine or by streptomycin and penicillin. Fever and other symptoms persisted in spite of the latter. He then resorted to treatment with chloroquine and observed a prompt recession of the symptoms. The temperature was soon brought down to normal, and healing of the abscess was claimed after a fortnight's treatment. Similar results were reported by Murgatroyd and Kent (1948) in their case of liver abscess, which had proved very resistant to emetine, di-iodohydroxy quinoline, streptomycin, penicillin, and local emetine lavages. More comprehensive work on the subject has been reported by Harinasuta (1950, 1951), working in Siam, where hepatic amoebiasis is of frequent occurrence. In his first paper he reported nine cases of amoebic liver abscess (two with pulmonary complications) successfully treated with chloroquine. Later he made a comparative study of the action of chloroquine and emetine in amoebic liver abscesses, putting 45 cases on chloroquine treatment exclusively and an equal number of cases on emetine. In conclusion, Harinasuta remarked: "In comparison with emetine, chloroquine appeared to possess as much curative value in the treatment of amoebic liver abscess. It might be somewhat inferior on the point of relapse rate; but in other respects it had its own advantages—e.g., peroral administration, tolerability, and low toxicity in general—so that it might be employed even in cases in which emetine was contraindicated." Among the side-effects of chloroquine Harinasuta listed nausea, vomiting, mild diarrhoea, transient pruritus, disturbance of ocular accommodation, and also a slight fall in the blood pressure. He noted, however, that these side-effects were usually mild and insignificant and only transitory in nature.

Among the publications by Indian research workers reference may be made to those of Sharma *et al.* (1951) and of Subramaniam (1951). The former reported on two cases of amoebic liver abscess from Bangalore which proved resistant to treatment with emetine, vitamin B-complex preparations, sulphonamides, and penicillin. At the time of chloroquine therapy the patients appeared to be so gravely ill that their chances of recovery seemed to be extremely small. The authors concluded: "Our impression was that the administration of chloroquine marked a turning-point in an otherwise downward course. Our cases are in line with the striking results by chloroquine reported by others, and the drug marks a definite advance in the treatment of amoebic hepatitis, especially cases with abscess formation." Subramaniam used chloroquine diphosphate only in four cases of amoebic hepatitis, but claimed good results with this exclusive treatment. He stated that in all cases the temperature subsided within 24 to 48 hours, there was a marked lessening of the pain, and the patient felt better.

Present Series

I have used chloroquine diphosphate ("resochin") in a series of 11 cases of amoebic liver abscess, and the results obtained seem to confirm the observations of others that this drug has advantages in the treatment of extra-intestinal infections with *E. histolytica*.

The patients were admitted to the King Edward Memorial Hospital or to the P.G. Singhanee Hindu Hospital, and were kept there throughout the course of treatment. They were asked to return if there were any symptoms suggesting relapse, and each was given a postcard to be filled in by a doctor treating him for the complaint. Each patient also received another card with particulars of the previous history and treatment given.

The diagnosis of amoebic liver abscess was based upon the history of the clinical signs and characters of the pus aspirated by liver puncture. One patient with enlarged tender liver, raised temperature, and leucocytosis was negative on aspiration; he was treated with chloroquine without success. Fluoroscopy was carried out to show the movement and elevation of the dome of the diaphragm and the condition of the lungs and pleura. In every case the blood was examined for evidence of leucocytosis and was repeated in some cases during the course of treatment. It was only after the diagnosis was established by aspiration of pus that treatment with chloroquine was instituted. Emetine was not given in any case. The dosage of chloroquine was one tablet (0.25–0.15 g. of base) twice a day, preferably after food, for a period of 10 to 12 days in the first six cases. After two of these cases had relapsed the length of treatment was increased to 30 days. The initial higher dosage advocated by Conan (1949) and used by most workers was not adopted because of the untoward reaction noticed in a case of amoebic hepatitis not included in the series. As Indians are of small size, the lower dosage was more likely to be tolerated, with fewer untoward reactions. The drug was given for a period of 30 days in a case of relapse. It was not administered by the parenteral route.

Eleven cases (nine male, two female) of amoebic liver abscess were treated during a period of two years. As there were rigid criteria for diagnosis, not all the cases of liver abscess were taken for study, particularly if there was any doubt about whether emetine had been given before or during hospital treatment. In some cases sulphadiazine and antibiotics were given for the lung and abdominal conditions. Details of the cases are shown in the Table.

Details of 11 Cases of Amoebic Liver Abscess

Case No.	Age	Sex	Result of Liver Aspiration	Stool Exam. for *E. histolytica*	Treatment Schedule		Day of Normal Temp.
					Daily Dose	Length of Treatment	
1	32	M	400 ml.	Neg.	0·5 g.	10 days	5th
2	45	M	200 ,,	,,	0·5 ,,	12 ,,	2nd
3	29	M	50 ,,	,,	0·5 ,,	12 ,,	3rd
4	46	F	50 ,,	Pos.	0·5 ,,	10 ,,	,,
			50 ,,	Neg.	0·5 ,,	2 ,,	Died 3rd day
5	40	M	600 ,,	,,	0·5 ,,	11 ,,	2nd
			100 ,,	,,	0·5 ,,	30 ,,	3rd
6	30	M	250 ,,	,,	0·5 ,,	10 ,,	4th
7	32	M	200 ,,	Pos.	0·5 ,,	30 ,,	3rd
8	37	M	400 ,,	Neg.	0·5 ,,	30 ,,	2nd
9	29	M	50 ,,	,,	0·5 ,,	30 ,,	,,
10	36	F	300 ,,	,,	0·5 ,,	30 ,,	3rd
11	44	M	200 ,,	,,	0·5 ,,	21 ,,	2nd

E. histolytica was found in the stools in two cases. The temperature subsided within 72 hours in most cases, and within 48 hours in five. In some cases in which the temperature was normal after aspiration of the abscess it did not rise after the drug was given. The patient felt better by the fourth day, and had an improved appetite. All patients gained weight—as much as 20 lb. (9 kg.) in a month in one case. A lessening of liver tenderness was the first sign of improvement, and the lower margin of the liver soon disappeared from below the costal margin. The leucocytosis subsided in about a week in those cases in which examinations were made. No attempt was made to measure any changes in blood pressure, as observed by Harinasuta (1950, 1951), but no overt effects of a lowered blood pressure were noticed. Apart from mild nausea in two cases and dimness of vision in one, toxic symptoms of the drug were not recorded. Nausea, gastro-intestinal irritation, itching, and changes in accommodation in the eyes were noted in one case (not included here) when the initial dose was double that used in this series.

Relapses

Two patients were readmitted with recrudescence of the disease, one of them three months and the other four months after treatment with chloroquine for 10 days. In both cases pus was again aspirated. One of them (Case 4) died two days after the second admission, before chloroquine had any chance of action. This patient had a pulmonary complication. Case 5 was again treated with chloroquine, 0.5 g. a day for four weeks, with complete success.

Harinasuta (1951) had 10 relapses in a series of 45 cases which responded to further chloroquine treatment—a relapse rate of 22.2%. They occurred after a two-weeks or a three-weeks course of treatment. In the present small series the relapse rate was two in six (33.3%) after 10 to 12 days' treatment at a lower initial dosage. Harinasuta observed a definite refractoriness to a single course of chloroquine in two patients, both of whom died. Similar drug-resistance has been recorded with emetine.

Discussion

Conan (1949) advocated a three-weeks course of treatment, and subsequent workers have more or less followed the same course with satisfactory results. More than one-fifth of Harinasuta's (1951) cases required a second course of treatment, as did two of the first six cases in the present series. Relapses occur also with emetine and require further treatment. In order to avoid relapse the period of treatment in the remaining cases was increased to 30 days—longer than that advocated by Conan. From published work it seems obvious that the drug has a definite curative action on amoebic liver abscess, and it is the impression of most workers, including myself, that it acts more quickly than emetine and without the latter's harmful effects. It can be given when the general condition of the patient is poor and when emetine would be contraindicated and even harmful. Unlike emetine, it has no general toxic action and can be given orally. The dosage and the length of treatment so far used by most workers, even though satisfactory in most cases, needs evaluation by further clinical trials.

Relapses occur more often with smaller doses of shorter duration. They occurred even with the dosage advocated by Conan. Harinasuta (1951) had to use as many as five three-weeks courses in one case. From this it is obvious that the dosage advocated by Conan should be increased in length to four or even six weeks, as the drug can be taken by mouth and has no major untoward effects on the body. Conan's three-weeks course may be adequate for amoebic hepatitis, but not in all cases of abscess. In the present series cases of abscess and not of hepatitis were treated, as the value of the drug in the treatment of undoubted cases of liver complication of amoebiasis had to be established.

Extended clinical trials with a good follow-up should be undertaken in order to evaluate the length of treatment with chloroquine in cases of abscess. At present the drug is not readily obtainable, but when it is freely available and cheaper such a trial would be possible. Harinasuta (1951) advocated a combined treatment with emetine. I consider, in the light of present available knowledge, that a prolonged course of treatment is all that is necessary. A therapeutic trial with chloroquine can safely be carried out in cases of liver enlargement in which diagnosis is doubtful, and liver abscess can be easily excluded by such a trial, without any of the harmful toxic actions which accompany emetine therapy.

Summary

Eleven cases of amoebic liver abscess, three with pulmonary complications, were treated with chloroquine diphosphate with very good results. The dosage was 0.5 g. a day. It was found that treatment for 10 to 12 days was adequate in four out of six cases: two relapsed, but responded to further treatment. In the remaining cases the drug was given for 30 days. One patient died during a relapse. It is suggested that further work

should be carried out in order to determine the dosage of the drug required and the length of its administration in the treatment of the abscess. Minor toxic symptoms were observed. The drug can be safely used as a therapeutic test if diagnosis is doubtful.

My grateful thanks are due to the Dean of the King Edward Memorial Hospital and to the Honorary Director of the P.G. Singhanee Hindu Hospital for facilities, and to Dr. A. G. Brooke, of Chowgule and Co. (Hind) Ltd., for a free supply of the drug.

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"DANGEROUS RECIPIENTS" OF TRANSFUSION

INCOMPATIBLE REACTIONS AFTER TRANSFUSION OF GROUP O Rh-NEGATIVE BLOOD

BY

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The following case reports are placed on record to re-emphasize that Group O Rh-negative blood is not free of potentially dangerous blood-group factors, and that inexperienced medical staff are not suitable persons to undertake the matching of blood for transfusion.

Case 1

A multiparous woman aged 26, known to be Group O Rh-positive, was delivered of her third baby by elective caesarean section. Because of haemorrhage during the operation a transfusion of 2 pints (1,140 ml.) of blood became necessary, and the house-surgeon "matched" two bottles of Group O Rh-positive blood against the patient's serum by a saline slide technique. No incompatibility was detected, but on the day after the transfusion the patient was noticed to be "slightly jaundiced." The baby also had developed a definite jaundice within a few hours of birth, but since the mother was Rh-positive and the baby's haemoglobin was 140% (20.7 g. per 100 ml.) the possibility that the mother's serum contained irregular blood-group antibodies was not considered.

Seven days later the mother's general condition was unsatisfactory and her haemoglobin 35% (5.2 g. per 100 ml.). Transfusion of a further 2 pints (1,140 ml.) of blood was therefore prescribed, and on this occasion the house-surgeon selected and matched 2 pints (1,140 ml.) of Group O Rh-negative blood, presumably as a safeguard against a haemolytic transfusion reaction. No incompatibility was detected, but the transfusion was discontinued after 1½ pints (850 ml.) had been transfused because the patient had developed a severe rigor. During the next 48 hours she had jaundice and oliguria. Although her haemoglobin remained at 35% (5.2 g. per 100 ml.) she refused any further transfusion and made a gradual recovery to normal health during the next six to eight weeks.

Laboratory investigations showed the patient's blood to be Group O Rh-positive, Rh genotype cDE/cDE, and that the transfused Rh-negative cells had undergone haemolysis. Immune antibodies, type anti-e + anti-C, were demonstrable in the patient's serum to a titre of 256 with homozygous e-positive red cells (Rh-negative cells, cde/cde) suspended in saline and in albumin. The titre against heterozygous cells (R_1R_2,CDe/cDE) was 64.

Inquiry into the patient's previous history revealed that she had been transfused with 4 pints (2,270 ml.) of blood (Rh group unknown) at her first pregnancy seven years before, because of a severe accidental haemorrhage, and was subsequently delivered of a stillborn macerated foetus. Her second pregnancy, three years later, had resulted in the delivery of a healthy female child who had shown "a slight jaundice" shortly after birth, but whose subsequent progress was uneventful. The third baby, the outcome of the pregnancy under discussion, was subsequently found to be Group A, R_1R_2 (CDe/cDE); a direct antiglobulin (Coombs) test on its red cells was positive, and by the twenty-ninth day of life its haemoglobin had dropped to 42% (6.2 g. per 100 ml.). After a transfusion of Group O blood of genotype cDE/cDE it made a satisfactory recovery.

Case 2

A woman who had had two normal children received an emergency blood transfusion (group unknown) during an air raid in 1941. Later she had one normal full-term child and then two miscarriages, each being a six-months foetus. At the age of 42 she was admitted to hospital because of menorrhagia. After a few days in hospital she had a sudden haemorrhage at night, and a resident house-surgeon transfused a pint (570 ml.) of Group O Rh-negative blood in emergency and without previous direct matching. At the same time another member of the resident medical staff "matched" a further bottle of Group O Rh-negative blood for her by a slide technique, but transfusion of this blood was found not to be necessary. Nine days later it was decided to transfuse this "matched" blood so that the patient might be made fit for curettage. She developed a rigor at the conclusion of this transfusion, followed by jaundice, haemoglobinuria, and oliguria for the next seven days.

Serological investigations demonstrated the patient to be Group O Rh-positive, Rh genotype CDe/CDe. Immune antibodies of the type anti-c + anti-E were demonstrable in the post-transfusion sample of her blood to a titre of 32 in saline and 256 in albumin against homozygous c-positive cells (Rh-negative cells, cde/cde), and 2–4 in saline and 16–32 in albumin against heterozygous c-positive cells (R_1r, CDe/cde). The patient's post-transfusion sample contained no Rh-negative cells, thus confirming that the blood transfused was incompatible.

Comments

Both these patients nearly lost their lives, and both suffered severe renal damage, because of the transfusion of Group O Rh-negative blood. Fortunately, although Rh-negative corpuscles contain the Rh antigens c, d, and e, and may contain other antigens such as Kell, Fya, and S, which are known to have been the cause of similar haemolytic transfusion reactions, few patients requiring transfusion possess the corresponding antibodies, anti-c, anti-e, anti-Kell, etc., in their plasma. In consequence incompatible transfusions from this cause remain a rarity. The fact, however, that immune antibodies of this type may be present in the circulation of certain patients, even on rare occasions, constitutes a challenge, and, by a more thorough applica-

tion of knowledge already well established regarding the hazards of transfusion therapy, accidents from this cause need not arise.

In neither of these instances was the transfusion of whole blood so pressing that advantage could not have been taken of existing laboratory facilities for blood-matching by trained laboratory staff. These cases serve as a reminder that this must be done whenever circumstances permit if the best service is to be given to the patient. As soon as plasma prepared during the war years was found to carry a risk approaching 10% of inducing hepatitis in the recipient, preliminary plasma transfusion whilst the matching of blood was being undertaken, or as the sole emergency transfusion for cases of moderate haemorrhage, wisely fell into disrepute. Now that the transfusion of "small-pool" plasma carries little greater risk of transferring the hepatitis virus than does a transfusion of whole blood, and, alternatively, satisfactory plasma substitutes, dextran and polyvinylpyrollidone, are available, we believe with Discombe (1952) that greater use should be made of such fluids for the avoidance of incompatible transfusions.

Immune antibodies active against transfused corpuscles of the patient's own ABO group are particularly likely to be present in the circulation of recipients who have had jaundiced or stillborn babies, or who have reacted adversely with a rigor, jaundice, or haemoglobinuria to a previous blood transfusion. Even in a dire emergency, therefore, such as a domiciliary "flying-squad" emergency, where the transfusion of unmatched whole blood may seem entirely warranted, strenuous efforts should be made to have blood specially matched against the patient's serum when there is a history suggesting the presence of immune antibodies. It is such patients that one of us (Tovey, 1950) has proposed should be termed "dangerous recipients," and in each of the above cases the patient's history would have placed her in this category.

Dangerous recipients run a particular risk in that if they are Rh-positive the immune antibodies they have developed may well be of the type anti-c or anti-e, and thus active against Rh-negative corpuscles (cde/cde). Or, should the recipient be Rh-negative with Rh antibodies (anti-D) in her serum, an Rh D-positive bottle of blood which has been misgrouped or mislabelled "Rh-negative" may give rise to a serious haemolytic transfusion reaction. Moreover, in some instances incompatibility from immune antibodies can be detected *in vitro* only by methods of direct matching which are too complicated to employ as a routine, such as an indirect antiglobulin technique or a titration procedure using bovine albumin. It is important, therefore, that clinicians obtain a history of the outcome of previous pregnancies or transfusions from any patient about to be transfused. Should the history indicate the patient to be a dangerous recipient, blood should not be transfused until it has been matched by the special procedures mentioned. Whenever possible, the danger in the event of an emergency transfusion should be anticipated, and as soon as it is known that a patient has given birth to a jaundiced or stillborn baby or has suffered a serious reaction to transfusion a full serological examination should be carried out to determine whether immune antibodies are present, and, if so, their exact type.

In neither of the above patients, although their histories indicated the need, had such serological investigations been made before the transfusion accidents. Although Gunz (1946) drew attention to the need for a standard history sheet to accompany every request for transfusion, and such a sheet has been employed by regional transfusion centres for the past six years, many hospitals are still not taking this precaution as a routine for their cases for transfusion.

Case 2 further illustrates that, although a patient may be transfused without serious reaction with blood of a certain ABO and Rh group, this does not mean that a later transfusion of blood of the same ABO and Rh group will be similarly unaccompanied by reaction. It is important to bear in mind that the transfusion of blood can result in the stimulation of dangerous antibodies, and any further blood for transfusion should invariably be matched on a freshly taken sample of the recipient's serum if more than 48 hours have elapsed since a previous transfusion.

We are grateful to Dr. M. Gillespie and Dr. J. S. Campbell, of the South-west Regional Transfusion Service, and to Dr. A. E. Mourant and Dr. D. Parkin, of the M.R.C. Blood Group Reference Laboratory, for help with the serological investigations.

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SENSITIVITY OF AUTONOMIC GANGLIA TO HEXAMETHONIUM IN HYPERTENSION

BY

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The introduction of hexamethonium bromide (H.M.B.) by Paton and Zaimis (1949, 1951) as a substance which blocks the transmission of nervous impulses across the synapses of autonomic ganglia presented a potentially valuable therapeutic means of controlling hypertension. The specificity of its action on autonomic ganglia makes it also a most valuable tool in the study of the autonomic nervous system, and this property is used here to study the underlying mechanisms producing hypertension. Repeated doses of hexamethonium bromide or bitartrate* are given intravenously, and the following points are observed:

(1) the sensitivity of the blood pressure to depression by autonomic blockade;

(2) the level to which the diastolic blood pressure may be depressed; and

(3) the dose required to affect the pupillary light reflex.

The first indicates the state of activity of the autonomic ganglia controlling blood vessels, and incidentally the suitability of patients for treatment. The second gives the minimal diastolic pressure which is used to differentiate various types of hypertension. This term is used in the sense defined by Frew and Rosenheim (1949), as the pressure maintained by the inherent tone of the blood vessels and circulating pressor substances, and corresponds to the term blood pressure "floor" of Ferris *et al.* (1948). Both of these authors used tetraethylammonium bromide (T.E.A.B.) to block autonomic ganglia.

Material

Tests were performed on patients who had been in hospital for at least seven days, and in one-third of the cases repeated tests were performed to establish the reliability of the method. The admission of patients to hospital was made for the investigation and treatment of hypertension or renal disease, and was quite independent of the present study. Cases with heart failure, extreme renal failure, or a history of recent thromboses were excluded.

The clinical diagnosis of essential hypertension was made after exclusion of other causes. Renal hypertension was assumed to be present if evidence could be obtained of

*All doses are expressed as those of the dibromide salt. Messrs. May and Baker kindly gave supplies of the bitartrate used in this investigation.

previous renal disease or associated toxaemia of pregnancy. In all cases a standard amylobarbitone sedation test (White, 1944) was performed, and in a quarter of the cases a test using T.E.A.B. was performed.

Methods

After a single injection of H.M.B. the effect on the blood pressure is found to be maximal within five minutes; repeated injections give a progressively diminishing effect. To minimize the effect of the biological variation in sensitivity to drugs a number of repeated doses were given in preference to a single standard dose. After a single injection it is also found that there is a transient overswing in the fall of pressure which exaggerates the fall in blood pressure particularly when larger doses are used. All blood-pressure readings are taken by the same person, using the auscultatory method and the diastolic pressure taken at the fifth phase—that is, as all sound disappears. This is necessary because the fourth phase often disappears when the blood pressure falls. Attention is paid to the diastolic pressure, as this gives more constant responses and the end-point can easily be defined, whereas the systolic pressure is more variable and sometimes shows a progressive fall in pressure.

The Test.—The procedure outlined gives reliable results and is free from complications. The patients, after being told precisely what is going to be done, are placed in quiet surroundings lying *absolutely flat* except for one pillow under the head for comfort. Blood pressures are taken every ten minutes until a resting level is established, when the first injection of 10 mg. of H.M.B. is given intravenously and pressures are read at three-minute intervals for 15 minutes. Thereafter injections of 25 mg. are made at 15-minute intervals until the maintained reduction in diastolic pressure does not exceed that of the previous dose by more than 8 mm. Hg. This is usually achieved by doses of 35–60 mg.—that is, second or third injections. The dose producing 75% of the fall in diastolic pressure is recorded as the *effective hypotensive dose.* If the blood pressure does not respond to a dose of 35 mg. it will not do so to larger doses. This was demonstrated by the additional doses it was necessary to give in order to block the ciliary ganglion. The dose at which the response of the pupils to light is slight and unsustained is recorded as the *effective pupillary dose.* When large doses (exceeding 85 mg.) are given there is sometimes a secondary slight fall in blood pressure. This is not closely related to the injections, and is partly accounted for by the onset of somnolence and the prolonged immobilization of the patient. For this reason, blood-pressure readings are taken at half-hourly intervals after the completion of the test until an upward trend of pressure is established. The results of some earlier tests in which there were minor variations in procedure have been used.

Precautions.—Mild fainting sometimes occurs when the first, and rarely the second, dose produces a profound and rapid fall in pressure. This is readily overcome by raising the foot of the bed. No patient has lost consciousness, and it has not been necessary to give pressor drugs. On three occasions when the blood pressure fell considerably after both the first and the second injection it was thought prudent to stop the test, although the patients did not complain of ill effects. Postural hypotension persists for a variable time after the test, and patients are not allowed out of bed or to sit upright in bed until the following morning.

In spite of a considerable reduction in blood pressure in some patients there has been no evidence of thrombosis occurring during the period of hypotension or afterwards. No symptoms due to the paralysis of other organs under the control of the autonomic nervous system were encountered.

Results

A total of 69 tests have been performed on 46 patients with hypertension, and in addition tests were carried out on a control series of 12 patients suffering from minor surgical disorders. According to the responses of the diastolic pressure to the test, the hypertensives can be divided into three groups (see Table).

Group A.—Eighteen patients in whom there was an appreciable fall of diastolic pressure (exceeding 14 mm. Hg.) to 90 mm. Hg or below. The mean fall in diastolic pressure was 28 mm. Hg (range 16–58) and the mean minimal diastolic pressure was 82 mm. Hg with a mean effective hypotensive dose of 25.8 mg. of H.M.B.

Group B.—Nine patients in whom the fall in diastolic pressure was at least 14 mm. Hg but remained above 90 mm. Hg. The mean fall was 28 mm. Hg (range 16–48) and the mean minimal diastolic pressure 104 mm. Hg with a mean effective dose of 37.7 mg. of H.M.B.

Group C.—Nineteen patients in whom the pressure remained within 14 mm. Hg of the initial level. To exclude the possibility that variations in sensitivity might account for the absence of response, repeated doses were continued in this group until an average dose of 110 mg. had been given. At these doses there was sometimes the slight fall in pressure already described, and this has been disregarded.

Throughout the entire series the reduction in the blood pressure was not related to the initial systolic, diastolic, or pulse pressures (Fig. 1). The initial resting blood pressures recorded show that the pulse pressure is related to the diastolic pressure and not to the age of the patient. The degree of response to the test was not determined by the clinical severity, as is illustrated by Fig. 2, in which the results of two similar cases are recorded. Group A contained the greatest proportion of cases of uncomplicated essential hypertension, while the nine cases of Group B appear to be more severe.

The average age in Group A was 53.1 years (only four being below 50 years) and in Group C it was 35.6 years.

Data of Controls and of Hypertensive Patients Divided into Three Groups According to Responses to Tests with Hexamethonium Bromide

	No. of Cases	Mean Age	Sex	Clinical Type of Hypertension	Mean Initial Blood Pressure	Mean Minimal Diastolic Pressure	Mean Fall in Diastolic Pressure	Mean Effective Dose	
								B.P.	Pupils
Controls ..	12	46·1 yrs. (s.d. 14·0)	M 4 F 8	None	118/64 mm. Hg	60 mm. Hg	4 mm. Hg		77 mg.
Group A ..	18	53·1 yrs. (s.d. 7·2)	M 5 F 13	Essential 13 Malignant essential 1 Renal 3 Malignant renal 1	186/110 „ „	82 „ „	28 „ „ (s.d. 11·1)	25·8 mg	76·7 „
Group B ..	9	43·6 yrs. (s.d. 10·3)	M 6 F 3	Essential 2 Malignant essential 5 Renal 1 Malignant renal 1	206/132 „ „	104 „ „	28 „ „ (s.d. 8·2)	37·7 „	83 „
Group C ..	19	35·6 yrs. (s.d. 11·6)	M 9 F 10	Essential 10 Malignant essential 3 Renal 2 Malignant renal 3 Coarct. aorta 1	188/112 „ „	107 „ „	5 „ „		82·6 „

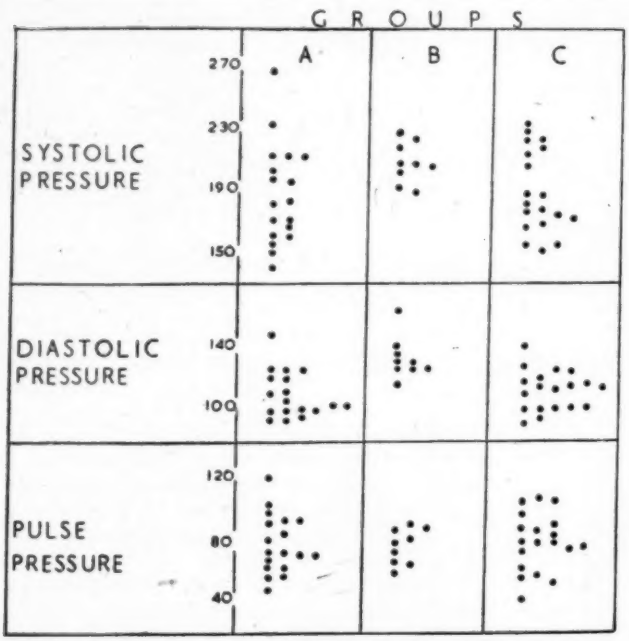

FIG. 1.—Initial status of 46 patients with hypertension, divided according to their responses to tests with hexamethonium. Group A—fall in diastolic pressure exceeds 14 mm. Hg and reduces it to 90 mm. Hg or below. Group B—fall in diastolic pressure at least 14 mm. Hg but remains above 90 mm. Hg. Group C—fall in diastolic pressure is less than 14 mm. Hg.

This difference was highly significant ($P < 0.001$), and was still valid when all cases of renal hypertension were excluded and essential hypertension was considered alone. The sensitivity of the blood pressure was not associated with that of the pupils. The effective pupillary dose in all groups was approximately the same (76.7–83 mg.).

Controls.—The control series of 12 patients showed an insignificant fall in diastolic pressure. There were no differences in the response of older and younger subjects. The average age of the group was 46.1 years. The effective pupillary dose was approximately the same as that of the hypertensive patients.

Repeatability.—To establish the value of the test 15 patients were given two or more tests, and in these the minimal diastolic pressure remained within 10 mm. Hg. Five patients had repeated tests over a period exceeding 12 months, the minimal diastolic pressure remaining at the same level in all except one, in whom it rose as the clinical state deteriorated. The effect of treatment with H.M.B. is found in general to follow that of the tests, a response being obtained in the blood pressure of patients in Groups A and B, but not in Group C. Prolonged treatment, however, with hexamethonium, or by sympathectomy, has not been found to affect the minimal diastolic pressure. In one patient, however, a strict rice diet which had been maintained for two months had a considerable effect on the minimal diastolic pressure, reducing it from 88 to 64 mm. Hg. A similar effect has been reported by Stead *et al.* (1948) using T.E.A.B.

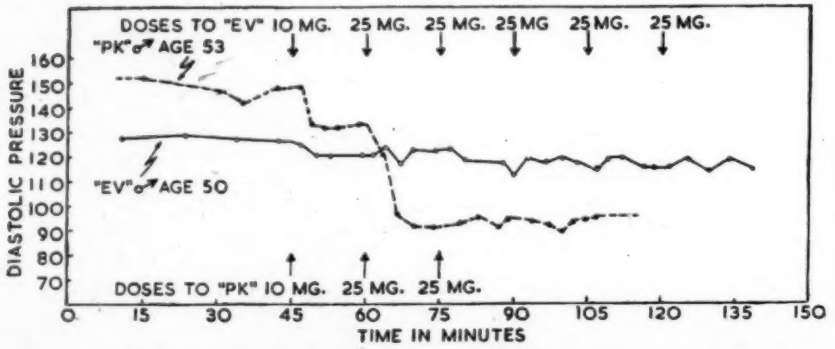

FIG. 2.—Response to hexamethonium test of two clinically similar patients, EV and PK, with malignant hypertension.

Discussion

Hypertension is a single physical sign of what is known to be a large group of diseases. The separation of these from one another is sometimes difficult because the raised blood pressure itself in time produces changes, particularly in the arteries, and treatment is usually required for these effects of the raised pressure and not for the cause. The test described offers a method of identification of those cases of hypertension in which the nervous system plays an important part. It is only by the separation of types that order can be introduced into this bewildering subject.

The appreciation of the part played by nervous factors in elevation of the blood pressure has been maintained in spite of evidence to the contrary (Pickering, 1936; Prinzmetal and Wilson, 1936), from the study of the variability of the blood pressure (Ayman, 1931; Alam and Smirk, 1943) and its response to rest in bed (Watkin *et al.*, 1950) and sedatives (Cady *et al.*, 1936). More recently this has been reinforced by the markedly depressor response sometimes obtained to drugs which block the activity of the autonomic nervous system—T.E.A.B. (Lyons *et al.*, 1948; Frisk *et al.*, 1948) and more recently hexamethonium. This drug, like T.E.A.B., reduces the blood pressure by causing arteriolar dilatation and has little effect on the cardiac output in the recumbent subject (Gilmore *et al.*, 1952). Evidence of the overactivity of sympathetic ganglia controlling the blood vessels is demonstrated by their marked sensitivity to blockade in contrast with the ciliary ganglion. The main effect on the blood pressure is achieved by a small dose (10-35 mg.) before transmission through the sympathetic ganglia is completely blocked, and at approximately one-third of the dose required to paralyse the pupils. Response to hexamethonium is therefore similar to experimental neurogenic hypertension, which is the only type of experimental hypertension responding to autonomic blockade by T.E.A.B. (Page, 1949; Page and McCubbin, 1951).

As the degree of vasoconstriction is represented by the fall in blood pressure it is inevitably somewhat exaggerated in these tests, since the neurogenic component is always removed at the highest initial pressure. The same degree of vasodilatation at a lower initial pressure would give a smaller reduction in pressure. Nevertheless a great fall in pressure, particularly if it then comes within the normal range, must indicate that the nervous system is the dominant though not necessarily the only aetiological factor.

The responses in clinically similar cases were found to be quite unpredictable, as there was no correlation with the signs by which the severity is assessed, and each group contained both mild and severe cases. The depression of blood pressure was compared with that of amylobarbitone sedation, and in 12 patients it was also compared with the response to T.E.A.B. Although the trend of the three tests was often the same, there were considerable quantitative differences between them, and each test would have resulted in a somewhat different classification in this series. There is likewise a broad correlation between results of the H.M.B. test and those of Frew and Rosenheim (1949) using T.E.A.B., and also of Frisk *et al.* (1948) and Lyons *et al.* (1948), with the difference that Frisk *et al.* and Lyons *et al.* both report a correlation between the response and the initial level of diastolic blood pressure.

The variability of the minimal pressure in a particular patient reported by Levinson *et al.* (1948) and Ferris *et al.*

(1948) using T.E.A.B. was not found. Stability of the minimal diastolic pressure suggests the relative independence of the nervous and humoral factors in hypertension. The striking difference in the ages of Groups A and C is the only factor with which the response to H.M.B. could be correlated, and it suggests the separation of elderly hypertensives into a distinct aetiological group.

Collateral evidence for this is found in the well-known differences in mortality of hypertension below and above 50 years (Bechgaard, 1946; Burgess, 1948), particularly as the incidence of hypertension increases so strikingly with age, rising from 5% in young adults to 30–40% after the age of 40, and thereafter increasing progressively with age (Master *et al.*, 1943). In contrast to the severity and frequency of changes in the renal arteries of young hypertensives, in elderly hypertensives the lesions have been shown to be mild, and only a little more severe than those seen in subjects of the same age without hypertension (Perera and Krane, 1951).

In the group which failed to respond to hexamethonium it is clear that the autonomic nervous system can play little part in the elevation of the blood pressure at rest, and in this they behave in the same way as experimental renal hypertension. It is concluded that the absence of a response in the case of coarctation of the aorta is evidence that a humoral mechanism is present in this condition.

The evolution of early labile hypertension into a sustained humoral one is not supported by the present findings, but the reverse seems possible. Subjects in the intermediate Group B and those with renal hypertension in Group A may tentatively be said to have had a nervous mechanism superimposed upon a humoral one.

Summary

Hexamethonium was used to investigate a group of 46 cases of hypertension. It was given in repeated doses to produce the maximal fall in diastolic pressure. The results show that the neurogenic component is present in elderly hypertensives and is very uncommon below the age of 50 years.

I acknowledge the co-operation of the staff of Charing Cross Hospital, Drs. R. A. Hickling, K. Shirley Smith, and E. C. Warner, who allowed me access to their cases of hypertension, and to Mr. E. A. Crook and Mr. L. A. Broster for allowing certain of their cases to act as controls. I also thank Dr. A. A. Osman for facilities to investigate cases of hypertension at the Renal Unit, Pembury Hospital, Kent, and Mr. K. Browne for checking the statistical material.

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TERRAMYCIN IN THE TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

BY

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It is generally agreed that procaine penicillin, in single daily injections of not less than 300,000 units, is the most reliable means of controlling acute otitis media in children with a minimum degree of supervision. Larger doses of crystalline penicillin at more frequent intervals increase the margin of certainty. Oral penicillin and sulphonamides are less reliable, but they offer advantages of administration which favour their use in certain cases. Lewis *et al.* (1952) assessed the value of chloramphenicol and aureomycin in this disease, but concluded that they were unsuitable for domiciliary treatment because, although as effective as penicillin against the organisms commonly found in acute otitis media, some children took such a strong aversion to them that it was impossible to maintain an adequate dosage.

With the advent of terramycin it was decided to review the position, as this compound appeared to offer certain advantages that might answer the need for an oral antibiotic effective in this disease. Terramycin has a wide range of antibacterial activity, and so far has been reported free from toxicity. It is reasonably stable in flavoured solutions, not unduly bitter to the taste, and can also be given in the form of sugar-coated tablets or capsules. In the absence of any published studies of the action of terramycin in otitis media and of an exact precedent for dosage, a clinical trial was made using 50 mg. of terramycin per kg. of body weight per twenty-four hours, against a control series of cases receiving penicillin.

Method

A two-page form was prepared, the first page containing the history, results of examination, type of treatment, and notes on the bacteriological investigation. The second page showed the patient's name only and a summary of daily progress. When a case of acute otitis media was accepted the necessary parts of the form were completed and the pages separated: the first was retained in the laboratory and the second in the out-patient folder. This was to ensure that the clinical observers (S. M. and A. B. H.), who saw each case from the second day onwards, had no knowledge of which antibiotic was being used for treatment and could therefore rely on the impartiality of their judgment.

All cases were first seen by the same casualty officer, well experienced in the recognition of the disease, who allocated the cases to their respective antibiotic in strict alternation. Myringotomy was performed, regardless of

antibiotic, if it was considered necessary to relieve tension. Penicillin was given in the form of "distaquaine," 1.2 ml. daily for five days; this contains 100,000 units of crystalline penicillin and 300,000 units of procaine penicillin. Terramycin was administered orally for five days in the form of a flavoured elixir, tablet, or capsule—the mode depending on the age of the patient. The daily dose was 50 mg. per kg. body weight split into three portions, one being given after each main meal. Five days was regarded as the minimum safe period of administration, for each antibiotic, to be reasonably certain of avoiding an unextinguished disease due to bacterial "persisters."

Results

Clinical.—The Table shows the effect of the terramycin treatment of acute otitis media in children in comparison with treatment with procaine penicillin. It will be seen

The Effect of Terramycin Compared with that of Procaine Penicillin in the Treatment of Acute Otitis Media in Children

Treatment Groups	Distaquaine (F)	Terramycin
No. of cases	33	35
,, ,, ears affected	42	44
,, ,, unilateral cases	24	26
,, ,, bilateral cases	9	9
Average days' duration before seen	2·6	4·0
Drums intact	34	30
,, perforated	8	14
Myringotomy required	16	9
Average days for:		
Relief of—		
Pain	1·4	1·4
Discharge	2·2	3·5
Ear to return to normal—		
Ear discharge, surgical or spontaneous	8·6	8·6
Ear never discharged	7·0	5·7
Failures	4	4
Mastoidectomies	0	0

that the results are comparable, the apparent failure rate—four cases in each series—being the same. On analysing the incidence of acute otitis media in childhood in relation to age in the 68 cases it was found that it was highest in the 6-year-old group. The Chart demonstrates the age/incidence relationship. It suggests that during the first school year exposure of the child to an alteration in its usual bacterial environment plays a part in the causation of this disease. The cases were equally divided between the sexes.

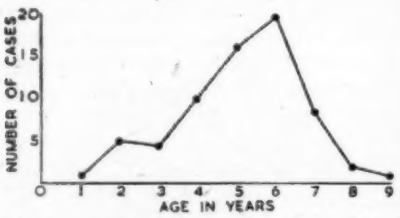

Chart showing incidence of acute otitis media in relation to age.

Bacteriological.—Two media were used, blood-agar and blood-crystal-violet agar plates, the second to suppress *Staphylococcus aureus* in order that any underlying haemolytic streptococci could be isolated. Meatal swabs taken as close as possible to the drum were inoculated on each medium.

No. of sterile swabs in presence of an intact inflamed drum		21
No. of swabs giving growth in presence of an intact inflamed drum		9
Coagulase-negative *Staph. albus*	4	
Diphtheroids	1	
Coagulase-positive *Staph. aureus* (1 penicillin-resistant)	4	
No. of swabs giving growth in presence of a perforated drum or after myringotomy		29
Haem. strep. in pure culture	14	
Coagulase-positive *Staph. aureus*	7	
Haem. strep. and *Staph. aureus* mixed	5	
H. influenzae	2	
Str. pneumoniae	1	

(1 strain of *H. influenzae* isolated was insensitive to penicillin)

All organisms isolated were tested for sensitivity to both antibiotics using the A.C.P. (1952) disk method. With the exceptions given above, all pathogens were sensitive to terramycin and penicillin.

Penicillin Failures

Case 1.—On the third day of treatment for otitis media of the left ear, acute disease set in on the other, healthy, side, and bilateral myringotomy became necessary. The course of penicillin therapy had to be extended to 10 days before the infection was brought under control.

Case 2.—This case was one of unilateral otitis, for which myringotomy was required. Haemolytic streptococci in pure culture were isolated from the exudate. Two days after the completion of treatment there was a recurrence in both ears, followed by perforation of the drums. A five-day course of terramycin was given, with return of the middle ear to normal.

Case 3.—This was a case of right otitis media with an intact drum. Five days after apparent satisfactory response to penicillin, otitis media recurred; this responded well to a course of terramycin.

Case 4.—Bilateral otitis media with perforated drums and a discharge from which haemolytic streptococci were isolated in pure culture. After five days' treatment there was still a copious discharge from the left ear (no growth obtained on culture). Terramycin therapy was then started, and led to a dry left middle ear with a small healing perforation.

Terramycin Failures

Failure in Cases A and B was due to refusal of the patient to take the antibiotic in any form, the refusals being apparently based on childish antipathy to "medicine."

Case C.—A case of unilateral otitis media requiring myringotomy. Three days after completing the terramycin course bilateral relapse occurred. *Staph. aureus* was recovered from the primary and relapse exudates. This organism was only moderately sensitive to terramycin, but was highly sensitive to penicillin. Substitution of the latter antibiotic gave satisfactory clinical response.

Case D.—A case of unilateral otitis media with a perforated drum and copious discharge from which haemolytic streptococci in pure culture were isolated, equally sensitive to terramycin and penicillin. After two days' terramycin treatment the discharge was sterile and showed signs of abatement. Fourteen days after completion of the antibiotic course there was a recurrence of exudate through the unhealed perforation. A course of penicillin then resulted in cessation of discharge in six days.

Discussion

Of the four failures in the penicillin-treated cases, three responded to terramycin. In the terramycin series, if the two which refused medicine are discounted, the balance of favour indicated by an assessment of the failures rests with terramycin. In all other respects there is little to choose between the antibiotics. We have experienced no real difficulty in administration, nor have we encountered unwelcome side-effects. Terramycin should thus prove a satisfactory antibiotic for domiciliary use, particularly in treating nervous, frightened children whose reaction to a hypodermic needle leaves one exhausted and dismayed at the future prospects, and in those cases in which daily attendance by a doctor or nurse is difficult or impracticable.

Summary

A clinical trial of terramycin in the treatment of acute otitis media in children is reported.

The results indicate that this antibiotic, at a dose of 50 mg. per kg. daily for five days, compares favourably with intramuscular procaine penicillin daily for the same period.

No real difficulty was encountered in the administration of terramycin. Toxic effects were not observed.

We are indebted to Dr. Ivor Marsh, late casualty officer, Belgrave Hospital for Children, for his interest and enthusiasm; to the Medical Research Council Antibiotic Clinical Trials (Non-tuberculous Conditions) Committee; and to Dr. R. K. Phillips, of Pfizer, Ltd., for supplies of terramycin.

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Medical Memoranda

Familial Cystinuria

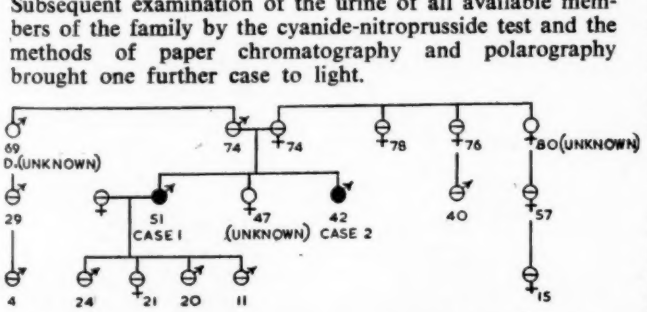
Cystinuria is an inborn error of metabolism in which the amino-acid cystine, together with lysine and arginine, is excreted in greatly increased quantity in the urine. There is also evidence that some cystine is excreted as a labile precursor of unknown composition which liberates cystine on standing. (In the absence of calculi, cystinuria is a symptomless condition.) The output of cystine is not increased by feeding this amino-acid, as it is excreted as a sulphate. However, if cysteine or methionine is fed there is an increased output of cystine. High-protein diets would therefore seem inadvisable. The factors responsible for keeping cystine in solution in the urine are not yet known, but calculus formation does not seem to be directly related to the concentration of cystine in the urine. It has been reported that solution of stones will take place if the urine is kept at a *p*H of 7.5 by administration of sodium citrate.

The occurrence of cystinuria in families has recently been reviewed by Dent and Harris (1951). In addition to the 11 families reported in the literature they have collected a further 11. As a result of their study they have put forward the view that cystinuria occurs in three types of case: (1) in the Fanconi syndrome, associated with many other amino-acids; (2) in Wilson's disease (hepato-lenticular degeneration); and (3) "classical" cystinuria, the type considered here, in which there is also an increased excretion of lysine and arginine: several of the cases of this type in the literature were, in their opinion, examples of the Fanconi syndrome.

In the past the detection of cystinuria depended mainly on the recognition of the typical hexagonal crystals of cystine in the urine or on the qualitative cyanide nitroprusside test. Lewis (1932) examined the urine of 10,534 students by the cyanide-nitroprusside test and found an increased quantity of cystine to be present in 1 in 600. It seems likely that the use of the newer and more sensitive methods of chromatography and polarography will bring more cases to light.

FAMILY HISTORY

The family reported here was discovered initially through the finding of cystine crystals in the urine of one member. Subsequent examination of the urine of all available members of the family by the cyanide-nitroprusside test and the methods of paper chromatography and polarography brought one further case to light.



The family tree, showing ages of members and presence or absence of cystine in the urine.

Case 1.—A retired coach-driver aged 51 was operated on for removal of bladder stones at the ages of 6, 14, and 25 years. He had a right nephrectomy for "staghorn" calculus in 1943. He was admitted to St. Mary's Hospital in January, 1951, for treatment of cardiac failure following myocardial infarction in May, 1948. On routine treatment he complained of a burning pain on micturition. Microscopical examination of the urine revealed cystine crystals. The cyanide-nitroprusside test was positive and paper chromatography showed an increased excretion of cystine, lysine, and arginine. An *x*-ray picture of the bladder showed two stones.

Case 2.—A younger brother (aged 42) of Case 1. There is no history of renal or cystic calculus. His only symptoms are those due to a peptic ulcer. Paper chromatography showed the same abnormal pattern of amino-acid excretion as in Case 1.

In both these cases polarographic studies (Reed, 1942) suggested that the output of cystine was about 0.5 g. a day. The range of output in normal persons is 40–80 mg. in 24 hours. In cystinurics the range has been given as 0.4–1.8 g. in 24 hours.

The investigations of Dent and Harris tend to show that classical cystinuria is inherited through a simple recessive factor or is a heterozygous condition with irregular manifestation. The family history reported here would fall into either of these forms of inheritance.

I am indebted to Dr. J. W. Litchfield for permission to publish this case report, and to Dr. H. Harris and Professor F. L. Warren for examining the urine by chromatography and polarography at University College, London.

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Blackwater Fever Treated with Cortisone

CASE REPORT

A Yoruba boy aged 19 months suddenly became ill at 11 a.m. on August 25, with a high fever, and was given an injection of quinine before admission to hospital the same day. He had been quite well, apart from having attacks of fever at varying intervals since birth, for which he had always received quinine. This treatment had apparently terminated the fever rapidly on each occasion.

On admission he was in a collapsed condition; his temperature was 104° F. (40° C.), his pulse 140 and of a poor volume, but he appeared to be well nourished. The mucous membranes were very pale and no icterus was noticed at the time. The heart was apparently normal. In the lungs scattered sibili were audible. The spleen was palpable three fingerbreadths below the costal margin, and the edge of the liver was just palpable. At 11.30 a.m. he passed 10 ml. of almost jet-black viscid urine, and methaemoglobin was demonstrated spectroscopically. The haemoglobin was 4.8 g.%, and a blood film showed large numbers of *Plasmodium falciparum* trophozoites. On August 26 he appeared to be moribund. The conjunctivae were icteric, and his general condition had deteriorated. By 3.45 p.m. only 1 oz. (28 ml.) of black urine had been passed since the last specimen was collected at 11.30 a.m. on the previous day.

Cortisone, 100 mg., was given intramuscularly, and at 8 a.m. on August 27 there was a noticeable clinical improvement: the child sat up and ate; his temperature was 97.2° F. (36.2° C.), and his pulse 94. He had taken 70 oz. (2 litres) of fluid in the past 24 hours and was known to have excreted 8½ oz. (240 ml.) although he had been incontinent since 3.45 p.m. on August 26. The first three specimens following the injection of cortisone were dark, but were lighter than previous specimens, and the next three

specimens appeared normal in colour. Cortisone, 100 mg., was again given intramuscularly. This was followed by a dose of 50 mg. on August 28 and 29. On the 30th he was sitting up; the conjunctivae were icteric, and there was slight oedema of the feet and face. No further cortisone was given.

The urinary output on August 28, 29, and 30 was about 20 oz. (570 ml.) a day, and some urine was voided into the bed; it contained no methaemoglobin. The anaemia was treated with iron, and the malaria from the outset with mepacrine. The child made an uneventful recovery and was discharged.

COMMENT

It is suspected that blackwater fever is a haemolytic disease occurring in those infected with *P. falciparum* and whose cells have been sensitized by quinine. As cortisone lowers the sensitivity of body tissues in certain allergic states (Carey *et al.*, 1950), it was given in the hope that it might reduce the sensitivity of the cells to the circulating haemolysin and relieve the renal cortical ischaemia responsible for the anuria.

Although the clinical state of cases of blackwater fever is known to alter rapidly, it was felt that the condition of this child on the second day was such that a fatal outcome was inevitable. Cortisone seemed to have had an effect in this case.

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Advantages of a Perineal Curve Applied to Midwifery Forceps

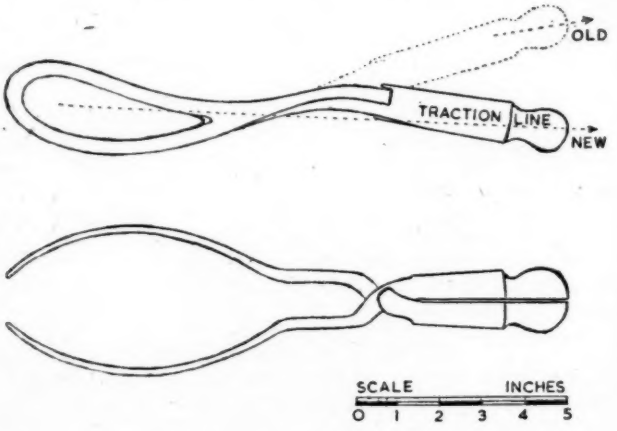
The first patterns of midwifery forceps—those of Chamberlen in the seventeenth century and of Edmund Chapman (1733) and William Giffard (1734)—were short and straight. William Smellie (1752) recommended the short straight forceps for general use, and he it was who discovered, to his great delight, how this instrument could be used for rotating the head in occipito-posterior presentations. Nevertheless, it was Smellie, too, who lengthened the forceps and added the pelvic curve in order to reach the head higher up in the pelvis—an invention also claimed for André Levret (1751) and Benjamin Pugh (1754). The pelvic curve was also an outstanding feature of the *mains de fer* designed by Palfyn in 1720. In the course of time the long curved forceps has supplanted the straight forceps for general use.

It was soon discovered that there were several disadvantages in the pelvic curve, notably the fact that traction on the handles is inefficient, as the direction of force is not in the axis of the birth canal. Many attempts to overcome this difficulty were made, and it was finally solved by Tarnier in 1877 with the axis-traction forceps. By the time axis traction became definitely established the necessity for the high forceps operation had vanished with the introduction of the relatively safe forms of caesarean operation in use to-day. The principle of axis traction still holds, but the patterns of forceps in general use are unnecessarily heavy and powerful for the low forceps operation, and many obstetricians have abandoned their use. Furthermore, with the long forceps with the pelvic curve, whether with axis-traction rods or without, it is not possible to obtain a good cephalic application when the head, in mid-pelvis or higher, lies in the transverse position. Severe lacerations of the birth canal have followed attempts to use the long curved forceps to rotate the head in this position, and most obstetricians in this country condemn the practice.

As long ago as 1769 R. Wallace Johnson, realizing some of the disadvantages of the long curved forceps, endeavoured to overcome them by bending back the shanks in a perineal curve, thus bringing the handles more into line with the axis of the blades. This was the first of many attempts to obtain axis traction without the use of additional apparatus. The well-known forceps designed by Kielland (1916) also has a perineal curve for the same purpose, and solves most of the problems of applying forceps to cases of deep transverse arrest, but it has not yet become very popular, probably because of certain other features which require a special technique to be practised if this instrument is to be used as Kielland intended.

During the winter of 1949–50 I had an old forceps of the Ramsbottom type replated, and took the opportunity of getting the shanks bent back at an angle of about 30 degrees, close to the lock (see Diagram). I have used this instrument now for nearly three years, and have found that the alteration exceeded my expectations in making the forceps more efficient and handy. A line drawn through the ends of the handles and passing through the centre of the fenestrae almost exactly corresponds in direction with a line drawn in the same way but passing through the traction crossbar of the Barnes–Neville axis-traction forceps I used formerly. The curve of the instrument as seen from the side very closely corresponds with the curve of the Kielland forceps.

I claim that the addition of a perineal curve in this way gives the following advantages over the ordinary long forceps: (1) It provides axis traction for all low forceps deliveries without the addition of any traction rods, and nearly as efficiently as that provided by the Barnes–Neville forceps. (2) It can be more easily applied to the foetal head in transverse positions, giving a proper cephalic grip. It could be used for rotating the head in much the same way as the Kielland forceps is used, though I have not yet tried it. (3) It is more convenient than the normal type for use on the aftercoming head in breech presentations, as the handles are bent away from the body of the child in the same way as those of Piper's forceps (Piper and Bachman, 1929). (4) It is an ideal instrument for the general practitioner, as it is more versatile and more convenient to carry.



I claim no originality in this instrument, the idea being nearly two centuries old. Peterson (1952) has described a very similar forceps, which he has used for over 100 deliveries with complete satisfaction, and claims much the same advantages for it. It is my view that a special instrument is not necessary, and that it will suffice to give a perineal curve to any standard instrument, such as Simpson's or Anderson's.

WALTER RADCLIFFE, M.B.

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Reviews

A REFUGEE DOCTOR IN ELIZABETHAN LONDON

Hamey the Stranger. By John J. Keevil. (Pp. 192. 21s.) Geoffrey Bles, London. 1952.

There were two Baldwin Hameys: the father—the "stranger"—that is, the alien (1568–1640)—and the son, the "Englishman" (1600–1676). Dr. Keevil has devoted a second volume to the son, who is remembered as a very successful practitioner and particularly as a generous benefactor of the Royal College of Physicians of London. The "stranger" attained no eminence and made little or no impact on the medicine of his day. He would hardly obtain mention in even the most detailed history of medicine, and was, professionally, no more than a reasonably successful and rather unreasonably conservative London practitioner.

And yet Hamey the stranger was well worthy of this memorial. It has been said that the true inner history of any life, however drab and ordinary it may seem, if properly told can be a topic of the most absorbing interest. But the life of Hamey the stranger, though outwardly undistinguished, was very far from being drab or ordinary. Dr. Keevil has told it with allusive charm. He has discovered many documents by or referring to the Hameys at the library of the Royal College of Physicians and, more unexpectedly, in the library of the University of Leyden. Nearly all of these papers are in Latin or Dutch, and their reading and translation was itself no mean task. But the secret of Dr. Keevil's power to arrest the reader's attention lies especially in his skilful use of the contemporary background as the setting of biography.

Hamey was born in Bruges of a family with Protestant sympathies. They suffered much from the acts of that monster of cruelty, the Duke of Alva (1508–83), in command of the Spanish forces that for years ravaged the Low Countries. In the terror which followed the year of Hamey's birth tens of thousands of innocent people were wantonly slaughtered by Alva's troops. Hamey's parents became refugees. They settled in Leyden, and Baldwin became a student in 1584 at its newly founded university. He was admirably taught by the eminent anatomist Pieter Paaw (1564–1617), himself a pupil of Geronimo Fabrizzi, Harvey's master, and by Jan Heurnius (1543–1601), an excellent and learned physician who stood for the simpler Hippocratic medicine against the pretentious Galenism fashionable at the time. Hamey was a devoted correspondent of Heurnius and of his son after him. Much of Dr. Keevil's material is drawn from Hamey's letters to these two.

In 1594, being now 26 and having failed to obtain a suitable post in Holland, Hamey accepted, on the urging of Heurnius, the position of personal physician to the Tsar of Russia. He set out for Moscow by the only practicable route, that via Archangel. Much of the interest of Dr. Keevil's book is the description, largely from the Hamey papers, of the conditions in Moscow in the years 1594–7, the domestic and foreign relationships of the reigning house, and the palace intrigues within the Kremlin. He detested the ignorance and bigotry, the suspicion and treachery, the squalor and cruelty and filth that were daily before his eyes. It was not long before he sought a way of escape, but that was by no means easy. Ultimately he obtained permission to go to Archangel to meet his affianced bride, who had ventured to follow him across the sea. The two escaped and sailed for London, where they settled in a house in the Tower ward of the City, from which Hamey practised.

The rest of the life of Hamey the stranger is the story of a refugee slowly and surely adapting himself to the conditions of the country of his adoption, but not without humiliation and opposition. At that time the Royal College of Physicians had the exclusive right of licensing any practitioner of medicine in and around London. Hamey had much difficulty in obtaining the licence, and was several times rejected by that body on grounds which seem now trivial, unfair, and quite unrelated to his professional competence. His ultimate success was substantial but in no way remarkable. The things that were remarkable about the man are, first, his firm and honest character, admirably backed by an able and devoted wife; secondly, the picture that he has left of the life of a refugee in Elizabethan and Jacobean London; thirdly, his Russian experiences; and, last and by no means least, the picture that he presents of the actual conditions of day-to-day practice. Very few practitioners have left such a record, and the history of medicine would be the richer for more. It is a moving story excellently told.

CHARLES SINGER.

RADIOTHERAPY FOR STUDENTS

X-ray and Radium Therapy for Students. By Basil A. Stoll, F.F.R., D.M.R.(Lond.), D.M.R.T.&D.(Eng.). Foreword by Frank Ellis, M.D., M.Sc., F.F.R. (Pp. 206. 17s. 6d.) London: H. K. Lewis and Co. 1952.

In his preface the author states that this book is intended as a guide to the place of *x* rays and radium in medical and surgical practice and that its concise format should make it of value to a wide field of students, postgraduate and undergraduate. It is certainly concise in that the diagnosis, pathology, and treatment—surgical and medical—of almost the whole field of malignant disease as well as of some other pathological conditions are discussed in a book of pocket size of 206 pages. But it seems doubtful if the book will serve as a useful guide to the place of radiotherapy in practice, and it may be misleading to students. Its conciseness does not allow of discrimination between the numerous facts and opinions set down. A useful list of references is appended.

B. W. WINDEYER.

DETECTING LIES

The Instrumental Detection of Deception: The Lie Test. By Clarence D. Lee. (Pp. 249. £2 7s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1953.

This book, written by an American police detective, shows again how the spirit of man can be attacked by mechanistic approaches. The lie detector depends on the fact that alterations of blood pressure, respiration, and pulse rate are greater in most normal persons when questions involving personal guilt are put to them. Psychiatrists and psychologists know there are many exceptions to this generalization: one false positive response quoted in this book was due to a suspect under examination seeing a girl start to undress and sunbathe through the police station window. And the author realizes that such tests alone would hardly stand up to critical examination in a court of law, although important information can be obtained.

The purpose of these methods becomes clearer, however, when it is frankly admitted that their real value in the hands of the American police who use them is to enable more confessions to be extracted from frightened and guilty people. If a suspect can only be convinced of the supposed infallibility of the test he can be more easily broken down. In 80% of cases giving positive results confessions were, in fact, extracted afterwards, and a description is given of how these confessions are best obtained from the victims. Even if the test is negative, the police may sometimes pretend it is positive in order to get a confession.

The history of "scientific" examination of religious or criminal suspects throughout the ages shows many general fallacies inherent in such methods. In the olden days examiners, and even the accused, came to believe in skin tests for witches, which we now know were merely the

physical stigma of hysteria often brought on by the tension of the examination itself. One would like to know more about experiments made in those wrongly persuaded of their guilt in a preliminary "grilling" and whether subsequent tests might not become positive by suggestion. Behind the Iron Curtain it is as wrong for the examiner to accept knowingly a false confession as it is in the U.S.A. But fear-provoking methods can also affect the judgment of all concerned in such work, and absurd confessions may come to be genuinely believed. There is no conclusive evidence that the lie detector eliminates this risk in an atmosphere so emotionally charged that the electric chair is often the issue at stake.

A chapter is devoted to the suggested use of the method as a deterrent in department stores, banks, industry, and the investigation of insurance claims. The author rightly points out that most people would be more careful if they knew the test was to be given as a routine. The reviewer was just beginning to think the whole question was hardly "cricket" by British standards, when a London insurance firm was stated in an American magazine article to be willing to reduce premiums for American banks where the entire staff was tested for dishonesty in the first year, and at least one-third of them each succeeding year. We hope this is not really true, or we shall soon find it happening here as we increasingly copy American business methods. Streamlined models might even be provided for hospital gate porters under the N.H.S. to stop the staff from pilfering.

WILLIAM SARGANT.

OPHTHALMIC PATHOLOGY

Ophthalmic Pathology: An Atlas and Textbook. By Jonas S. Friedenwald *et al.*; with the editorial assistance of Helen Knight Steward. (Pp. 489; 240 illustrations. £4 10s.) Published under the joint sponsorship of the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology. Philadelphia and London: W. B. Saunders Company. 1952.

A book on ophthalmic pathology running to 477 pages larger than quarto is an event in ophthalmic literature. Sponsored as it is by the American Academy of Ophthalmology and Otolaryngology and the Institute of Pathology of the U.S. Forces, expectation runs high. It carries, in fact, not only the authority of the two sponsoring organizations, but also that of two previous publications, for it is based on the *Atlas of Ophthalmic Pathology*, first published in 1938 by the Ophthalmic Registry of the American Forces, and the *Pathology of the Eye* brought out by Friedenwald in 1930. The dual origin of the present volume is also apparent in the format in which it now appears, for half the book is taken up by plates—contributed by Helenor C. Wilder (who was also responsible for the illustrations in Friedenwald's book)—while the text is devoted to general discussions rather than to histological descriptions. The preface by Dr. W. L. Benedict indicates that, though many authors have contributed to the book, Friedenwald and Maumenee are mainly responsible, and it would appear that its preparation began in 1945.

The text itself follows the usual mixed anatomical and aetiological classifications, but contains in addition lucid chapters on anatomy, physiology, histology, and senescence of the eye in relation to pathological lesions. Clinical discussions are introduced here and there, and these are not always relevant or illuminating. While the text is generally competent, the bulk of the chapters on congenital and developmental anomalies, and the heredo-familial and degenerative diseases, are disappointing; they even include such monstrosities as "atavism." The illustrations—some 1,000 figures on 240 plates—are well chosen and beautifully reproduced. In themselves they fully justify publication of the book, but the legends are open to criticism. In the original atlas full case reports were given; here they have been replaced by more useful short descriptions, but occasionally there is little more than a heading without any explanation of the details shown. It is also unfortunate that the text appears to have been written without any relevance to these excellent illustrations, so that the volume is in fact two books bound under one cover. It is to be hoped that the next edition will be a happier synthesis, even if drastic revision of the text is necessary with more emphasis on histopathology, for the book could be a landmark in ophthalmic literature.

ARNOLD SORSBY.

CONSTRUCTIVE MEDICINE

Man and Epidemics. By C.-E. A. Winslow. (Pp. 246. £1 5s.) Princeton, New Jersey: Princeton University Press. London: Geoffrey Cumberlege. 1952.

Do you have a son of years enough to be lured towards medicine? Be you student health worker, family doctor, consultant, or of epidemiological persuasion, this book will stir the mind and warm the heart. Some readers, finding pleasure in half-forgotten fact, will pause to wonder that works written for the non-expert can be so much more expertly informative than erudite expositions. Others, perhaps for the first time, will evaluate their contribution to past events and to those events which are in the making. All will be led towards a reasoned perfecting of medical principle and practice. Be warned that, once begun, this book will not be laid aside.

For 50 years Dr. Winslow has been engaged in preventive medicine, or, as he prefers to call it, constructive medicine. Now he is professor emeritus of public health at Yale, and one is grateful not only for his long and continuing contribution to medicine but also for his years of receptiveness in humility and with humanity. His chapters are on such things as the history of disease concepts, water supply, milk, sewage, food hygiene, and insects in relation to disease. To the cynic these may be the subjects of old-time public health, subjects made strangely less worthy by their passing into common acceptance and usage. It is from the past, however, and from these subjects, that Dr. Winslow, with drama, logic, and perfect lucidity, develops and poses a concept for the future. The reader is informed in the preface that Dr. Winslow may follow this volume with other works on preventive medicine. May they be indeed forthcoming.

J. M. MACKINTOSH.

STUDY OF TWINS

Studio dei Gemelli (The Study of Twins). By Luigi Gedda. Preface by Professor Cesare Frugoni. (Pp. 1,381; 548 figures. 15,000 lire.) Rome: Edizioni Orizzonte Medico. 1951.

A monograph covering the biological and other aspects of twinning in creatures ranging from plants to man is something for which there is an unquestionable demand. This book is an attempt to satisfy it. Two chapters are on twins in art, legend, history, and science. The excellent reproductions of paintings and sculpture, from Etruscan times to the present, and quotations from Plautus to Aldous Huxley enrich these most illuminating chapters. A chapter on comparative "gemellology" gives the layman a broad outlook on how complex is the problem of twinning and how useful twins may be as a tool in research. The bulk of the text is on twinning in man—incidence, causation, genetics, and embryology, twin pregnancy, and the anatomy, physiology, pathology, and psychology of twins. A full chapter summarizes the original work of the author on the similarity of glutathione levels in the blood of twins and their rhythmical variation. The significance of this contribution is not easy to assess on the basis of the data supplied.

The book is illustrated by a wealth of photographs and excellent colour plates, which accounts for its price. It is a pity that shortcomings of presentation and of critical selection, together with a lack of conciseness, reduce the value of the book considerably, the compilation of which must have required a large amount of work.

G. PONTECORVO.

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ORAL PENICILLIN

When penicillin is given by the mouth only a proportion of the dose, varying from about one-quarter to one-tenth, is absorbed, and various antacids, capsules, tablets, oils, and other devices to protect it against destruction by gastric acid increase this proportion little if at all. Moreover, the amount absorbed varies inexplicably from one person to another, and even in the same person at different times. It is thus not surprising that oral administration is often condemned—except in young children, for whom it has obvious special advantages—as both extravagant and unreliable. It nevertheless has its advocates. Binns,[1] reviewing the literature of the subject, concludes that oral penicillin in four-hourly doses of 400,000 units before meals should be satisfactory for fully sensitive coccal infections. Like all others who have reached such a conclusion, he qualifies it by recommending an initial intramuscular dose for seriously ill patients and by restricting such treatment to patients whose life is not in danger. Oral administration is also considered inadvisable for syphilis, deep-seated suppuration and osteomyelitis, bacterial endocarditis, and any infection due to an organism less sensitive than a pneumococcus, haemolytic streptococcus, or gonococcus. Elsewhere in this issue (p. 806) Dr. David Wheatley reports encouraging results in acute infections of the middle ear with combined oral penicillin and sulphadimidine.

The only insuperable objection to oral penicillin is the inconstancy of its effect, and according to Boger and his colleagues[2] much more consistent and sustained blood concentrations can be secured by giving probenicid (" benemid ") at the same time to delay renal excretion. According to these authors' findings 300,000 units of potassium penicillin with 0.75 g. probenicid given every eight hours has an effect equivalent or superior to that of 300,000 units of procaine penicillin injected intramuscularly once daily.

It also seems that more consistent effects can be obtained from a different form of penicillin, although this was first introduced for quite another type of use. We referred recently[3] to the introduction of a penicillin compound of low solubility, N,N'-dibenzylethylenediamine dipenicillin (known also as " penidural " and benzethacil), after a single intramuscular dose of which penicillin may be detected in the blood for as long as one month. This compound is also available in a form for oral administration, and the results of administering this to 101 children at the Great Ormond Street Children's Hospital are reported on page 805 by Drs. I. A. B. Cathie and J. C. W. MacFarlane. A standard dose of 300,000 units was given, and after a single dose a therapeutic blood concentration was invariably found after three hours. When the dose was repeated at six-hour intervals a cumulative effect was observed, with continuous maintenance of a therapeutic concentration. These authors remark that this is " the first oral preparation which has in our experience been reliably absorbed in 100% of patients." The effects of this preparation have also been tested in normal adults by Bayne, Gylfe, Carfagno, and Boger,[4] who controlled their observations by " cross-over " tests with the same dose of potassium penicillin. The effect of giving probenicid at the same time was to increase the concentration of penicillin in the blood at two hours and sustain it for some hours thereafter. These findings show that what is now known in the U.S.A. as an adequate " penicillaemia " can regularly be maintained by this combination of drugs. But it is a little puzzling that a penicillin compound of such low solubility—with consequently a slow rate of absorption when injected—should be absorbed quite rapidly and regularly when swallowed. Neither of these papers discusses the mechanism of absorption, and it would be interesting to know something about this. Nothing yet published shows whether this compound acts as such or only, as with penicillin esters, after breakdown.

Ideas about oral penicillin evidently need revision, and in this process ease of administration and diminished risk from sensitivity reactions will be given due weight. On the other side of the scale must be weighed the greater risk of indiscriminate use and of inadequate treatment when an infection is due to a less sensitive organism. The possibilities of self-medication when bottles of such preparations find their way into households also need to be considered, particularly if it should become known that a mouthful at the right time is a preventive of most forms of venereal disease.

[1] *Practitioner*, 1953, **170**, 273.
[2] *Antibiot. and Chemother.*, 1952, **2**, 555.
[3] *British Medical Journal*, 1953, **1**, 207.
[4] *Amer. J. med. Sci.*, 1953, **225**, 190.

THE ACCUSED RUSSIAN DOCTORS

We print in this week's *Supplement* a statement issued by the council of the World Medical Association on March 27 in Lisbon on the case of the nine Russian doctors recently accused of grave malpractice—indeed of the murder of some of their patients—and of acting as spies for the U.S.A. and Britain. The statement is restrained in tone, and no attempt is made to prejudge the issue. The last paragraph implies that the W.M.A. Council doubts whether the judicial procedure employed in the case of the nine doctors was such as to establish the truth, or at least in a way to convince those outside the U.S.S.R. On April 4 an astonished world learnt that the new regime in Russia declared that the accusations were false and arrived at "through the use of methods of investigation which are inadmissible and most strictly forbidden by the Soviet law," according to the statement published in *Pravda*.[1] The nine doctors, and six others unnamed, have been released. The W.M.A. Council made its protest on behalf of the 700,000 doctors throughout the world belonging to its constituent member associations. Whether or not it had any effect in Moscow, the W.M.A. has done well to voice its anxiety about the fate of doctors in a country which has no medical organization affiliated with it.

What are the facts? On January 13 of this year the Tass Press Agency in Moscow released a press statement which began thus: "Some time ago the security organs of the State discovered the existence of a terrorist group of doctors who had set themselves the goal of shortening through medical sabotage the lives of active functionaries in the Soviet Union." Nine medical specialists were named as belonging to the group, the majority of them apparently being Jews. Through allegedly wrong diagnosis and treatment they were accused of causing the death of Zhdanov and Shcherbakov, and of attempts against the health and life of five highly placed officers in the Russian armed forces. These accusations were arrived at on the basis of "documentary evidence, of investigations and conclusions arrived at by medical specialists, as well as on the basis of the confessions of those arrested." *Pravda* of January 13 elaborated the accusations in terms meant to leave the reader in no doubt of the guilt of the nine doctors, the majority of them allegedly "recruited by a branch of the American intelligence service—the international, Jewish, bourgeois-national organization 'Joint.'" Three of the doctors were accused of being agents of the English secret service. "In front of the whole world," stated *Pravda*, "the true face of the slave-owners and man-eaters from the U.S.A. and England has been revealed."

From January 13 to April 4 these were the facts presented to the world in the Russian press and broadcast widely over the air. As doctors we felt disturbed by this assault upon the professional integrity of our Russian colleagues, and especially by the probable effect of the accusations on the trust patients universally have in the sanctity of the doctor-patient relationship. As members of one of the learned and liberal professions we were alarmed at this renewed threat to civilized values in the anti-Semitism implicit in the charges and echoing the anti-Semitism of the Prague trial at the end of last year. But now the tables have been turned with a vengeance. The accused are released with a clean bill of legal health. The accusers are now accused. The unhappy Dr. L. F. Timashuk, the woman doctor who informed against her colleagues, has had taken from her the Order of Lenin bestowed on her on January 20 for this act. Such a *bouleversement* creates a feeling of both relief and bewilderment. As *The Times* puts it: "Surely there is no precedent in Soviet history for this public admission of fraudulent and evil methods in the State police and judicial system." If this violent loosening of tension between Russia and the non-Communist world is to be more than a nine-days' wonder, we may hope to renew those contacts with Russian doctors that began during the war. The B.M.A.'s invitation of hospitality to individual Russian doctors still stands. The World Health Organization refused to look upon Russia's withdrawal from it as permanent. The World Medical Association, we understand, has informed the Russian medical profession of the First World Conference on Medical Education to be held in London this year in August. If their delegates come to it they will be welcomed. Their colleagues from all over the world want to meet them, to exchange views, to share experiences, to get rid of mutual suspicions in mutual and friendly intercourse. Is it too much to hope that this may yet be possible?

A HAPPY EVENT

Women in labour owe much to the events of April 7 one hundred years ago. The *Court Circular* of that date contained the following announcement:

"Buckingham Palace, April 7.

"At ten minutes past one o'clock this day the Queen was safely delivered of a prince."

This referred to the birth of Prince Leopold, Duke of Albany, Queen Victoria's eighth child. And it was the administration of chloroform to the Queen during her son's birth that did so much to dispel the

[1] *The Times*, April 6, 1953.

[1] *Association Medical Journal*, April 15, 1853, p. 318.
[2] *Lancet*, May 14, 1853, p. 453.
[3] *Association Medical Journal*, May 27, 1853, p. 450.

prevailing religious and professional objections that made childbirth a needless misery to many women.

In reporting the happy event, this *Journal* (then called the *Association Medical Journal*)[1] remarked that "there are circumstances connected with the event which have likewise imparted to it no small degree of medical importance. We refer to the employment of chloroform having been sanctioned by Her Majesty's Physician in Ordinary, Sir James Clark, Her Majesty's First Physician Accoucheur, Dr. Locock, and Her Majesty's other Physician Accoucheur, Dr. Ferguson; to its having been administered by Dr. Snow; and to the fact of the Queen and the infant prince having gone on favourably from the first." After recording that "the Queen expressed herself as grateful for the discovery of this means of alleviating and preventing pain," the account went on:

"The responsible position, and the acknowledged skill of the physicians who sanctioned the inhalation of the chloroform, the Royal Majesty of the patient, and the excellence of her recovery, are circumstances which will probably remove much of the lingering professional and popular prejudice against the use of anaesthesia in midwifery, even when sanctioned by competent authority, and induced with requisite precaution. It is for this reason that we chronicle the recent accouchement of Her Majesty as an event of unquestionable medical importance."

The mention of professional prejudice comes as a surprise to the reader to-day, but it found forceful expression in the editorial columns of the *Lancet*[2]—uncharacteristically behind the times. "Intense astonishment," wrote our contemporary, "has been excited throughout the profession by the rumour that Her Majesty during her last labour was placed under the influence of chloroform, an agent which has unquestionably caused instantaneous death in a considerable number of cases. Doubts on this subject cannot exist." The article was concerned to draw a distinction between the necessary use of chloroform as an anaesthetic during surgical operations and what it considered to be its unnecessary use to ease the pangs of normal labour. The *Journal* report, it seemed, was hardly to be believed:

"Probably some officious meddlers about the Court so far overruled Her Majesty's responsible professional advisers as to lead to the pretence of administering chloroform, but we believe the obstetric physicians to whose ability the safety of our illustrious Queen is confided do not sanction the use of chloroform in natural labour."

A fortnight later[3] the *Journal* fired a parting shot at the *Lancet* for casting doubt on the accuracy of its original report and expressed its "own humble opinion" that

"the cautious inhalation of the vapour of chloroform during labour is entirely free from danger, and calculated to afford merciful relief from pain, in one of the most agonizing trials of humanity."

John Snow lived to see this "humble opinion" gain wide acceptance—more emphatically than it would to-day—and attended Queen Victoria again, for the birth of Princess Beatrice in 1857. He died aged only 45 the following year, when appeared his classical monograph *On Chloroform and Other Anaesthetics.*

HEALTH SERVICE INQUIRY

Noisy protests broke out on the Opposition benches last week when the Minister of Health announced that a committee was being set up to inquire into Health Service costs. But obscured in the rancour clothing Mr. Bevan's observations was one of special interest to the medical profession. He complained that the issue of Health Service economies was a matter primarily for the House of Commons and for political decisions, and criticized sending to a committee of inquiry "a matter which is at the centre of British politics." Most doctors agree that one of the most unfortunate features of the Health Service is that it started—under Mr. Bevan's aegis—at the centre of British politics and that it has never gravitated far enough away from that thoroughly unsuitable point. Mr. Bevan's successors, whether Labour or Conservative, have done something to remove the Health Service from the political arena. Clearly it can never be wholly withdrawn from it while it remains a State service. But there are many details in its finance and administration that should be free of political dispute and subject only in the most formal way to political decision. If the new committee is to be seen as a further endeavour to treat the issues non-politically, then it is to be welcomed for that alone. The Government would surely not be so inept as to appoint a committee of this sort merely to prepare the ground for destructive economies.

Given enough powers the committee should discover some much-needed information. It is asked to review the present and prospective cost of the Health Service, and to advise how a rising charge on the Exchequer can be avoided while providing for the maintenance of an adequate service. Dr. Ffrangcon Roberts has done much to show, both in this *Journal*[1 2] and in a book published last year,[3] how the cost of medical care has risen, goes on rising, and will continue without limit if allowed to do so. Various checks have been put on it, and the most effective may prove to be the dental charges. This is not to say that precisely similar charges can or should be imposed elsewhere. But, if it is agreed that stability

1 *British Medical Journal*, 1949, 1, 293
2 Ibid., 1952, 1, 321.
3 *The Cost of Health*, 1952, London.

is best achieved by proper design of the Service rather than by panic cuts and arbitrary limits, then a committee of inquiry is a move in the right direction. And if the committee is a non-political one only Mr. Bevan and his associates are likely to complain.

The question of block grants to hospitals is apparently to be inquired into—belatedly, the medical profession would add. The present financial methods, quite apart from the irksome restrictions the Treasury imposes when employing them, defeat their object in actually encouraging waste. In withholding that greater measure of independence that block grants would confer on hospital boards, the existing methods impair the sense of responsibility that surely ought to accompany public administration. Yet, when Mr. Macleod said that many people had for a long time considered that block grants were a matter which should be inquired into, there were cries of "No" from the Opposition benches. It is not clear whether they were denying the undoubted fact that many people thought the subject should be investigated or whether they were denying that such an inquiry ought to be held. In any case these dissentients will find no support for their views anywhere in the Health Service.

Whatever the nature of the committee (its chairman is a distinguished economist with experience of arbitration disputes), we may hope that it will fully consult the medical profession in the course of its inquiry. In the past too many Government actions have been decided—at times plotted seemed a better word—behind closed doors in Whitehall. An impartial committee can now do much to dispel the mistrust that is noticeable in the Service, and may help to give a better sense of direction and unity of purpose to all concerned with the nation's health.

ATTACK ON POLIOMYELITIS

An experimental vaccine against poliomyelitis has been prepared in the U.S.A. and its effects studied in human beings. According to Dr. J. E. Salk and his colleagues, who report[1] this important advance, the results are encouraging, but "should not be interpreted to indicate that a practical vaccine is now at hand." It seems that antibody against all three immunological types has been induced by inoculation of the vaccine.

Behind the preparation of this vaccine lies a multitude of experiments on the recognition, isolation, and culture of poliomyelitis virus strains. Ever since Landsteiner[2] transmitted poliomyelitis to monkeys the search has gone on for a more convenient laboratory animal for poliomyelitis research. However, strains of the virus, with the exception of a few capable of causing disease in rodents (Lansing, Type II), are pathogenic only to the primates. Attempts to adapt poliomyelitis virus to tissue culture in the past were largely unsuccessful in that no conclusive evidence was obtained of *in vitro* virus multiplication, except where primate tissue was used. A report by Sabin and Olitsky[3] in 1936 on the cultivation of the virus in human embryonic brain (later confirmed[4]) suggested that the choice of tissue would be limited. Many of the original disadvantages of tissue culture, often technical in nature, have now been overcome. The use of antibiotics has virtually eliminated bacterial contamination, a major obstacle to success before the last war. And the idea of using human tissue for culture, as suggested by Goodpasture and Anderson[5] for the growth of zoster virus, offered new lines of approach to the study of viruses affecting man.

Although the essential lesion in poliomyelitis is neuronal, primary multiplication of virus probably occurs in extraneural tissues. In 1949 Enders, Weller, and Robbins[6] at the Children's Hospital, Boston, using tissue culture of human embryonic material, demonstrated that poliomyelitis virus would multiply in neural and non-neural tissues and also in completely differentiated infantile skin.[6] In a series of recent communications Enders and his colleagues[7 8 9] have shown with abundant clarity that tissue culture is no mere technical exercise but a method of great practicability and even greater possibilities.

Two well-known methods have been found successful in growing all three immunological types of virus. The one is flask culture, when tissue fragments are suspended in a balanced salt solution; the other is roller-tube culture, when tissue fragments are embedded in a plasma clot and covered by salt solution. Opinion is hardening in favour of roller-tube culture as the method of choice.[9] The selection of tissue for cultures presents certain difficulties. Human embryonic, uterine, and renal tissues among others have given good results but have obvious limitations. Material removed at necropsy is not satisfactory, and growth in species other than man and monkeys has not been observed.[8] Monkey testicular tissue supports growth well and in many laboratories will be found more practicable.[10 11 12] A recent observation by Ledinko and Melnick[13] that testicular tissue from immune and non-immune monkeys is equally satisfactory suggests that serum antibody plays little part in determining *in vitro* susceptibility. Similar observations have been made on other viruses,[14 15] and it will mean that adult human tissue need not necessarily be obtained only from subjects whose immune state is known. Protein-containing cell stimulants are invariably incorporated into the fluid phase in the roller-tube method to ensure good cellular outgrowths. A move

1 Salk, J. E., *et al*, *J. Amer. med. Ass.*, 1953, **151**, 1081.
2 *Sem. méd.* (*Paris*), 1908, **28**, 620.
3 *Proc. Soc. exp. Biol.*, (*N.Y.*) 1936, **34**, 357.
4 Enders, J. F., *et al.*, *Science*, 1949, **109**, 85.
5 *Amer. J. Path.*, 1944, **20**, 447.
6 Weller, T. H., *et al.*, *Proc. Soc. exp. Biol.* (*N.Y.*), 1949, **72**, 153.
7 Robbins, F. C., *et al.*, *Amer. J. Hyg.*, 1951, **54**, 286.
8 Weller, T. H., *et al.*, *J. Immunol.*, 1952, **69**, 645.
9 Robbins, F. C., *et al.*, ibid., 1952, **69**, 673.
10 Syverton, J. T., *et al.*, *Proc. Soc. exp. Biol.* (*N.Y.*), 1951, **77**, 23.
11 Ledinko, N., *et al.*, *Amer. J. Hyg.*, 1952, **55**, 323, 339.
12 Younger, J. S., *et al.*, ibid., 1952, **55**, 291, 301.
13 *Proc. Soc. exp. Biol.* (*N.Y.*), 1952, **81**, 144.
14 Andrewes, C. H., *J. Path. Bact.*, 1930, **33**, 301.
15 Goodpasture, E. W., and Anderson, K., *Arch. Path.*, 1940, **30**, 212.
16 *Proc. Soc. exp. Biol.* (*N.Y.*), 1952, **81**, 208.
17 Wood, W., *et al.*, ibid., 1952, **81**, 434.
18 Enders, J. F., *et al.*, *Fed. Proc.*, 1952, **11**, 467.
19 Salk, J. E., *et al.*, ibid., 1952, **11**, 480.

towards simplifying the nutrient medium—and this is indeed welcome—is suggested in a report by Melnick and Riordan[16] that such protein stimulants can be replaced by an enzymatic protein hydrolysate. Furthermore they obtained excellent yields of virus when the roller-tubes were kept stationary. Reports on the use of synthetic media have also been made.[17] Evidence of multiplication of poliomyelitis virus in tissue culture can be shown by recognized methods of animal inoculation.[8] Simpler and equally reliable evidence can be obtained from the degenerative changes seen in cellular outgrowths (cytopathogenic effect) and by alteration in cellular metabolism with decreasing acid production (*p*H differential test).[8]

Tissue culture offers tremendous possibilities in research not only into poliomyelitis but into other virus diseases primarily infecting man, such as the acute exanthems. With the antibiotic era in full swing, direct isolations can be made from human material (faeces and brain) and the method extended for epidemiological surveys. How to treat or control disease is the ultimate aim of investigation, and the adaptation of poliomyelitis to tissue culture is a signal advance in this direction. Repeated passage of virus in tissue culture reduces its virulence to monkeys with no loss in tissue culture infectivity.[18] Inactivated vaccines have been found antigenic in experimental animals[19] and now in man.

WORLD HEALTH

The publication of the annual report[1] of the Director-General of the World Health Organization closely coincides with World Health Day—April 7—which many of the member States now officially celebrate, some by proclaiming it a public holiday, others by holding meetings and exhibitions designed to increase local interest in preventive medicine and in the advantages that accrue from international co-operation. The practical benefits of such co-operation are plainly set out in the report. W.H.O. is the great co-ordinator of public health work. Not only are backward countries helped to combat malnutrition and such endemic diseases as malaria and yaws, but the Western nations also gain from W.H.O.'s work on the biological standardization of drugs and other therapeutic substances, from its thorough investigation of B.C.G., and from the information being gathered by the World Influenza Centre in London—to mention only a few of the projects in which W.H.O. is interested. The amount of money available last year to finance all its activities came to between 7 and 8 million dollars—not a vast sum in these days of astronomical spending. Lack of trained workers has led to difficulties all over the world, but during 1952 more awards of training fellowships were made than in any previous year—1,147 as against 662 in 1951.

In his foreword to the report Dr. Brock Chisholm states that "the whole organization has now passed through its formative period. Its general policies and procedures and its relationships, both internal and external, have been established." That they should have been so soundly established is largely due to Dr. Chisholm himself. Five years ago he was appointed the first Director-General of W.H.O., and he retires in a few months' time. The report for 1952 is the last he will make to the World Health Assembly, and he has taken the opportunity to comment on one of the difficulties which faces any organization whose purpose is to help all the peoples in the world and not just some of them. To do its job properly the World Health Assembly must have unprejudiced advice, and members of its executive board ought to feel themselves responsible to the Assembly alone, and not to Governments or other bodies. Any Government unwilling to allow independence to the members it designates to the executive board should refrain from making designations, and members of the executive board who find themselves unable to act independently should resign. "Nothing short of complete world-mindedness is acceptable in any member of the executive board," writes Dr. Chisholm. In all the fields of international endeavour perhaps only in that of health could such an idealistic conception be stated with such confidence in its practicability.

[1] *The Work of W.H.O.*, 1952. Published by the World Health Organization, Geneva.

BETTER FACTORIES

Sitting between two fat men to keep warm on his journey to work 50 years ago, the man who recalls[1] this experience found strikingly different conditions on arrival at his factory from what is afforded to-day. Then dirty, rat-ridden, cold, and ill-lit, many factories provided neither a healthy climate to work in nor safe machines to tend. The great and beneficial changes wrought by legislation and changing opinion during these years are reviewed at length by the Chief Inspector of Factories in his latest annual report, and if better plumbing, brighter illumination, and purer air were sufficient to man's working needs his contentment at work could never have been deeper than it is now. But there have been other changes too, though they barely come within the report's scope. "A good example of British, and especially Birmingham, methods of production during the years" is the bicycle industry. Formerly one skilled man assembled one bicycle or made a complete handlebar. Now he "adds one screw as the article passes on a conveyor belt."

All the same, such improvements as the report recounts are exceedingly welcome, though a special cause of concern is the accident rate. Unfortunately, statistics are inadequate for comparisons back to 1901, nor are the numbers exposed to risk clearly known in any year. There were 828 fatal accidents in 1951, which was 29 more than in 1950. But the number of non-fatal accidents fell by 5% to 182,616, which was the lowest total recorded since 1938. The number of accidents connected with transport continued to rise, and the report comments: "While it is not to be expected that the widespread introduction of mechanical methods of handling and transportation would be unaccompanied by an increase of accidents of this kind, a rise of the order of 250% over 1939 is extremely serious." No

[1] *Annual Report of the Chief Inspector of Factories for the Year 1951.* 1953. H.M.S.O.

doubt the use of these new machines has averted many accidents—and more serious accidents—that would have resulted from the contact they often prevent between workmen and other machines that chop, press, saw, and so on. The stricter discipline among users of the new machines that the report calls for would reduce the accident rate, but that is only one of several ways in which the problem is being attacked. Clearly the design of machines as nearly foolproof as possible is desirable, and much work has been done on that in recent years. Again, industrial psychologists are aware that employment too far below a man's intellectual capacity is detrimental to him. Lack of interest will lead to lack of attention; to attribute the resulting accident to lack of discipline is only part of the story.

Perhaps the greatest change noticeable in the last 50 years—certainly to the workpeople themselves—is the reduction of working hours in a week. The Factory and Workshop Act of 1901 allowed a working week of 60 hours for women and young persons in non-textile factories (in textile factories 55½ hours). It was during the first world war that the effects of fatigue on production were first scientifically studied, and partly because of these studies, partly because of changed social attitudes, the 48-hour week came to be recognized as normal in 1918. During the 'thirties the five-day week became popular; since the second world war it has been worked almost everywhere, and with it the mid-morning tea break has come to stay. But how best to enjoy his leisure may be hard to learn for a man who at his work spends every minute, hour, day, and year adding screw after screw.

CANCER OF STOMACH AND BLOOD GROUPING

The search for relationships between blood groups and susceptibility to disease has not as yet proved very fruitful, and attempts to find an association with cancer have been inconclusive. In 1942, for example, Schinz[1] showed the frequencies of ABO groups among 1,000 patients with malignant neoplasms from the Röntgeninstitut at Zurich to be 430 of group O and 456 of group A, compared with 402 and 480 respectively among 1,000 patients with non-malignant conditions, the differences being not quite statistically significant. Now the findings of Professor Aird and his colleagues in cancer of the stomach, reported at page 799 of this issue of the *Journal*, are likely to provide fresh stimulus to such studies. The ABO blood-group distributions of 3,632 patients with cancer of the stomach in a number of hospitals in England and Scotland were compared with those of control groups of people in the same hospitals or localities. In respect of all but two of the Birmingham, Leeds, Liverpool, Manchester, Newcastle, and Scottish hospitals equal numbers of controls were taken at random from cross-sections of patients in the same hospital, and for the other two hospitals estimates were made from the data of the local blood-transfusion centres. In London 1,340 patients with stomach cancer were compared with the blood-group frequencies in Discombe and Meyer's series of 10,000 from north-west London.

Comparison of the distributions in Scotland, the northern towns of England, and London showed no important differences for the B and AB groups, but group A was more frequent and group O less frequent in patients suffering from cancer of the stomach than in the general population of the same locality, and this difference was present in every hospital from which data were obtained. In Scotland the percentages of group A were 36.4 for patients with cancer and 32.5 for controls; in the northern towns they were 46.4 and 39.3 respectively; and in London they were 46.0 and 42.2. Statistical tests showed the differences to be highly significant. In agreement with this, some hitherto unpublished figures for 704 patients with stomach cancer in Basle reported to the authors by Dr. Holländer showed 53.1% of group A compared with 45.1% among 4,518 controls. It may be noted that this relation is in the reverse direction to that reported from Zurich for cancer of all sites as quoted above, and this suggests that similar studies for other varieties of cancer would probably give very different results.

Interesting as these findings are, their effect on cancer rates for whole populations can be only slight. And a little calculation shows that, even if two populations existed having such unlikely extremes as 25% of group A in one and 65% in the other, the cancer rates would not differ by as much as 10% because of this genetic difference. The authors are at pains to point out that the association with blood grouping, far from accounting for the observed excess of stomach cancer mortality in English northern towns, tends to increase the divergence, which has to be explained, it would seem, by environmental factors not yet identified. The northern town populations have a smaller proportion of group A and would therefore be expected to have slightly less cancer of the stomach. Neither could racial blood-group differences, whatever they may be, go any distance towards accounting for the excess of stomach cancer mortality in North Wales compared with neighbouring English rural areas, which over the last 30 years has been of the order of 70% after allowing for all the local factors capable of assessment at the present time, such as differences in the verification of diagnosis.

The relationship between blood groups and cancer of the stomach shown by the statistics of Aird and his colleagues leads them to conclude that "it is no longer possible to regard blood groups A and O (in adults) as entirely devoid of selective value." The validity of this conclusion depends on the validity of an assumption, tacitly made, that a blood group can never be changed by cancer or by extrinsic factors causing cancer. This cannot be regarded as certainly true until it has been properly tested; and, if it should prove to be incorrect, an explanation of the statistical relationship might be found in a common cause.

[1] *Erbarzt*, 1942. **10**, 209.

Sir Russell Brain was re-elected President of the Royal College of Physicians of London on March 30. He was first elected President of the College in 1950.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE MANAGEMENT OF LATE AND LATENT SYPHILIS*

BY

G. L. M. McELLIGOTT, M.A., M.R.C.S.

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The rapid and sustained decline in early infectious syphilis that has taken place in most parts of the civilized world since the end of the war has not been accompanied by a similar fall in the incidence of latent and late infection. In England and Wales the number of these patients attending the treatment centres was higher in 1950 than it was in 1946. With the growing awareness among medical practitioners of the possibility of late and latent infection, and the rapidly growing practice of routine antenatal blood testing, it is likely that still larger numbers of these patients will be discovered in the future, and that we will be increasingly concerned in their management and treatment.

Dangers of Latent Syphilis

The ultimate importance of a disease depends upon its power to shorten life, and syphilis, especially when untreated in its early or asymptomatic stages, is well known as a not uncommon cause of premature death. I have always believed, however, in common with many colleagues both at home and abroad, that the lethal hazards of untreated syphilis, considerable as they may be, are not so great as is popularly supposed, and that in the patient who receives reasonable and fairly prompt treatment they are usually minimal.

The legacy of undetected syphilis, especially in women, that follows a war is bound to be considerable, though we now know that most of the gloomy prophecies about the fate of the untreated thousands during the first world war have not been fulfilled. To-day the growing practice of routine antenatal blood testing is doubtless averting many tragedies, and it seems a pity that these tests do not yet form part of the routine medical examinations of hospital out-patients and in-patients, candidates for life assurance, soldiers and sailors on discharge from National Service, and that these are not performed on those contemplating marriage. Though prompt treatment of the comparatively few cases of early syphilis that we now see, and, of course, of their consorts, is important, the death rate from syphilis during the next 30 years will depend largely on the discovery and treatment of the thousands who must still be at large in the as yet asymptomatic stage of late syphilis, and it is sometimes the doctor's duty to risk personal unpopularity by insisting on the examination and testing of spouses, children, and sometimes of parents.

Obvious late activity in syphilis is almost always preceded by a period of apparent latency, and it is during this time that we can do so much to arrest permanently, and in many cases cure, the still hidden chronic inflammatory process.

Diagnosis

The diagnosis of latent syphilis is one of exclusion, and is always difficult, and sometimes impossible, to make with accuracy. It will depend upon the skill and experience of the physician, on negative results of radiological examinations of heart and great vessels, on examination of the cerebrospinal fluid, and upon the verification by repetition of unexpected positive blood findings. Clerical or technical errors are still the commonest causes of so-called "false positive" serum reactions. Latent syphilis is never an emergency, and, once neurosyphilis and established cardiovascular disease have been excluded, the danger of delaying treatment for weeks or months is negligible. The notion of treating in order to "play for safety" is nearly always, except in pregnancy, bad medicine and will inevitably confuse the ultimate diagnosis. It is sometimes difficult to persuade the patient that more or less prolonged observation without treatment is necessary if his case is to be properly assessed, but it can be done, and he will appreciate it in the end.

In many cases of late or latent syphilis—possibly in the majority—one cannot even guess at the duration of infection. We are, perhaps, too much inclined to date it to the years of early adult life, or to the period spent in the armed Forces. Occasionally we are deceived; the middle-aged, or even the elderly, do contract syphilis, and primary and secondary signs frequently pass unnoticed in women. Also, the possibility of congenital infection can never be overlooked, and classical stigmata are often absent.

Telling the Patient

When a diagnosis has been reached, the question arises—What is the patient to be told? The answer is, the truth. All, except the very old, or some rare cases of mental instability, must have the facts, as the doctor sees them, carefully explained. The word "syphilis" must not be avoided and vague allusions to a "blood condition" or some such indefinite euphemism must not be substituted in its place. If this frank truth-telling is not done, the necessity for prolonged observation after treatment will be difficult to justify. I have been impressed by the bitterness with which patients have spoken of doctors who had failed to tell them the truth in a mistaken attempt to spare their feelings.

The significance of sero-resistance, and, indeed, of its probability, in spite of adequate treatment, should be explained as soon as possible to all patients who are in any way capable of understanding. If this is not done at an early stage the patient will inevitably associate a persisting positive blood reaction with a lack of response to treatment, and will consequently become either dissatisfied with his physician or apprehensive about or even despairing of his condition. In latent syphilis, perhaps more than in any other chronic condition, the doctor can afford to be optimistic, and it is surely his duty to be so. The findings of the United States Co-operative Clinical Group, which are in line with the experience of many of us, suggest that even without treatment only 20% to 30% of latent syphilitics would develop later manifestations of disease, and that treatment, even of the most moderate nature, would reduce this chance to one of from 2% to 5%. Such a risk is surely minimal when one considers the everyday hazards of life.

Late syphilis, especially when asymptomatic, must not be allowed to spoil lives, but only too often it does so. The medical curse descends upon the unfortunate patient in no uncertain manner, so that much of his outlook and many of his ambitions are conditioned by the knowledge that he is a syphilitic, and a man apart. Victims of far more serious conditions are more optimistic and less depressed by their diseases than are many adequately treated latent syphilitics. This is largely because a venereal infection is so essentially a secret between patient and doctor, and because secrets weigh heavily on many minds.

Treatment

Few will deny that the treatment of late syphilis has been, and perhaps sometimes still is, notoriously unsatis-

*From a paper read before the International Congress of Dermatology, 1952.

factory. Many physicians, often obsessed by the bogy of persistently positive blood reactions, have traditionally insisted on years of treatment with arsenicals and bismuth, which was only terminated by the collapse of the patient's health from the toxic effects of the treatment, of his morale from anxiety, and not infrequently of his bank balance. Though at least another decade must pass before the results of penicillin in late syphilis begin to be known with certainty, an encouraging indication of its probable effect is already provided by the results in neurosyphilis. In the great majority of patients treated, sustained improvement in the spinal fluid occurs, and, provided that irreversible structural damage to brain or spinal cord has not yet taken place, clinical results are much more impressive than after malaria and arseno-bismuth treatment and are, moreover, more rapidly attained. It is perhaps significant that certified deaths in England and Wales from dementia paralytica declined from 585 in 1943 to 167 in 1950, and those from tabes dorsalis from 313 in 1943 to 123 in 1950—a far more rapid fall than has ever before been recorded in so short a time.

Penicillin and Cardiovascular Syphilis

In this country there has been until recently a certain reluctance to use penicillin in cardiovascular syphilis, mainly because of exaggerated fears of the Jarisch–Herxheimer reaction. Cardiovascular syphilis is often not diagnosed until irreparable harm has been done, and, though even then quite a modest amount of treatment will probably heal the chronic inflammatory process, the resulting structural damage to the aortic wall or valves may inevitably shorten life. I am, however, becoming increasingly convinced that prompt intensive treatment with penicillin will in most cases, by halting the inflammatory process, improve the prognosis and help to prolong life. Earlier diagnosis, rather than better treatment, would seem to be what is wanted for the successful management of this condition. These views are supported by the work of Dr. J. H. Stokes and his colleagues in Philadelphia, who have recently reported the results of treating over 100 cases of various types of cardiovascular syphilis with penicillin alone during the last five years, and it is interesting to note that in this series no evidence of significant therapeutic shock or vasculo-toxic effect was forthcoming, neither were any certain cases of therapeutic paradox encountered. The penicillin was well tolerated even by the decompensated heart, and clinical improvement, particularly of anginal pain, was noted in a high proportion of cases. In the autumn of 1947 I decided to abandon the arsenicals in the treatment of syphilis in all its stages, and up to the present I have had no cause to regret my decision. Bismuth I retained in a modest total dosage of 2–4 g. until two years ago, not so much because I was attracted by the idea of consolidation treatment with a drug whose treponemacidal power fell so far behind that of penicillin, but because I believed that many patients would default from subsequent observation if the treatment time was so short as to bring it into contempt.

Dosage of Penicillin

At this stage it is hard to say how much treatment is necessary in the late or latent stages of syphilis. My present opinion is that, though it certainly should not be less than that recommended for early infections, it may one day be found to be not much more. Careful post-treatment observation with retreatment of considered failures or relapses is, in my view, far more important than the blind, continuous, so-called "insurance" therapy so popular in the past. I would commend without prejudice the idea of following an initial intensive course of six to twelve million units of penicillin, lasting from ten to fourteen days, with not more than two courses each of ten twice-weekly injections of 900,000 units of procaine penicillin in oil with aluminium monostearate (P.A.M.). I am convinced that each one of these injections will be far more therapeutically active than the fullest dose of any arsenical or bismuth preparation, and, which is perhaps more important, that it can do no harm.

It is perhaps as a preventive of congenital syphilis that penicillin has had its greatest success, and it is now established that as little as eight to ten days' intensive treatment of a syphilitic pregnant woman will almost always ensure that her infant is born free from disease. The expectant mother whose blood tests have proved positive on routine examination can thus be assured of her baby's safety, and every effort should be made to allay her anxiety.

Conclusion

In conclusion, I would restate my belief that in penicillin we have the most powerful, as well as the safest, treponemacidal agent yet known; that the progress of the disease can in most cases be rapidly and effectively halted by its intelligent use; and that its true value in late and latent syphilis will be certainly known only when careful clinical, cardiographic, and pathological observations (to include always examination of the cerebrospinal fluid) become general practice and when post-mortem study of treated cases becomes the rule rather than, as at present, the comparatively rare exception.

Next Refresher Course Article.—"Injuries to the Back," by Mr. E. A. Nicoll.

THE HEALTH OF SCOTLAND

SOME ENCOURAGING FIGURES

The 1952 reports of the Department of Health for Scotland and of the Scottish Health Services Council were published last week in one volume. The most striking improvement in the country's health was the decline in mortality from respiratory tuberculosis. The provisional rate of 27 per 100,000 (1,404 deaths) is the lowest figure yet reached for Scotland, and compares with rates of 37 in 1951, 47 in 1950, and 60 in 1949. The reduction was apparent in all age groups of both sexes, except males at the extremes of life. The highest mortality was still among young women, but even here there has been a remarkable fall: for women aged 20–24 the rate fell from 122 in 1950 to 45 in 1952, while for those aged 25–30 it was reduced from 124 to 46. The death rate from non-respiratory tuberculosis, at 4 per 100,000, was also lower than ever before. These encouraging figures were due to "improved medical and surgical treatment, together with the fact that the disease is now being brought under treatment at a much less advanced stage." By the end of 1952 the number of hospital beds in Scotland for respiratory tuberculosis had risen to 6,098, and the waiting-list had fallen to 1,711. To help ease the waiting-list over 400 tuberculous patients have been sent to sanatoria in Switzerland.

The provisional infant mortality rate fell to the record low figure of 35.2 per 1,000 births. A disturbing feature of the mortality in the pre-school years (1.5 per 1,000) is the high place taken by accidents. The principal causes of death among children aged 1 to 4 years, in order of frequency, were accidents, tuberculosis, pneumonia, and infectious diseases. Of the accidents, roughly one-half were caused by motor vehicles.

The Hospitals and General Practitioners

In 1951 the Department of Health published the Scottish Health Services Council's report on "The General Practitioner and the Hospital Service," and this has been studied by both the department itself and hospital boards. The Department of Health has this to say about the integration of the work of general practitioners with the hospitals:

"Some progress has been reported as regards direct access by general practitioners to hospital ancillary departments—for example, laboratory and radiology. There are signs that difficulties may arise in recruiting sufficient full-time hospital staff in some of the intermediate grades, and this factor may encourage the

wider use of general practitioners (especially former registrars) as part-time members of hospital staffs. Generally it seems true to say that the hospital boards are alive to the importance of establishing the closest possible link between the family doctor and the hospital service."

Size and Cost of the Health Service

About 64,000 persons are wholly or partly engaged in the Health Service in Scotland. Nurses and midwives (25,000) and hospital domestics (22,500) form the largest groups, then come doctors (5,300), administrators and clerical staff (4,000), and pharmacists (2,800). There are 1,400 dentists and about the same number of medical auxiliaries, and lastly 900 opticians. Last year about half the doctors were in general practice, there being 2,439 principals (of whom 1,280 were in partnerships) and 306 assistants. In the hospitals there were 750 consultants (372 of whom were whole-time) and 330 S.H.M.O.s (219 whole-time).

The general-practitioner services cost £5.37m. (excluding a back payment under the Danckwerts award of about another million pounds). Of this sum, £83,000 was paid in grants under the trainee assistants scheme and £20,000 as inducement payments. There was a small fall in the number of prescriptions compared with the previous year (from 20,787,000 to 20,371,000), but the average cost of each prescription rose from 5s. 1d. to 5s. 4d. during the year. The slight fall in the number of prescriptions is ascribed partly to the absence of any major epidemic, such as influenza, and partly to the 1s. charge. In all, the pharmaceutical services cost just over £5m. The supplementary ophthalmic service accounted for a little over half a million pounds.

Public Health Matters

Vaccination of children under 1 year against smallpox declined a little during the year, and is still far short of the desirable minimum. "Figures of the order of those shown in recent years (under 30% of the children of that age) do not afford adequate protection of the community." Immunization against diphtheria continued at a high level, although the 1952 figure for primary inoculations showed a decrease. There were eight deaths from diphtheria during the year, all in children who had not been immunized.

Another sign of the times was the continued decline in the number of domiciliary births, both absolutely and in relation to the total number of births. Steps now being taken to adjust maternity benefit rates in favour of the mother who is confined at home may perhaps alter this.

Apart from the subjects mentioned above, the Department of Health's report also deals with welfare services, food hygiene, water supplies and sanitation, housing, and town and country planning.

Scottish Health Services Council

Among the matters inquired into by the Scottish Health Services Council were the future duties, responsibilities, and status of medical superintendents in Scottish hospitals and the serious shortage of almoners in Scotland. At present, out of an estimated 500 almoners required for a complete service, there are only 75 employed. The council's recommendations for relieving the shortage are to reduce the cost of training by making it possible for a complete training to be had in Scotland, and secondly to create a new category of worker intermediate between the almoner and her clerical assistant. The position of these "almoner assistants" would be analogous to that of the assistant nurse. This proposal runs counter to the recommendation of the Cope Committee on Almoners.[1]

The council also initiated an inquiry on co-ordination in the field of child health. While it proved possible to make some specific recommendations, such as that more hospital beds should be provided for children, the general feeling was that it was too soon after the appointed day for a full review of the subject.

[1]Reports of the Committees on Medical Auxiliaries. Cmd. 8188. H.M.S.O.

Nova et Vetera

FRANCOIS RABELAIS, M.D.

Born about 1495, Rabelais died 400 years ago on April 9. He spent his youth in a Franciscan monastery until, renouncing holy orders, he entered the faculty of medicine at Montpellier. Here he gained the distinction of being the only person to lecture on Hippocrates and Galen from the original texts, for Rabelais was an enthusiastic humanist who studied the classics avidly.

Some say he was the first to dissect the human body. If not the first, he was certainly one of the first, using criminals who had been hanged. As a result of his demonstrations, it is recorded in the archives at Montpellier, the medical school was allowed two criminals a year for dissection instead of one every sixteen years or so.

Rabelais could never stay in one place for long. He left Montpellier and went to Lyons, then the centre of the printing industry in France, where he was employed as a proof-reader, putting to good use his knowledge of Greek. It was here he published his first medical work—*Epistolae Medicinales Manardi*—an annotated translation. Manardi was a doctor at Ferrara, and Rabelais translated his treatises, pointing out at the same time that the doctrine of *magister dixit* should not be followed too faithfully. In direct opposition to most medical men of the time, he thought the advancement of medicine and science should be viewed with an open mind. Later he published the lectures he had given at Montpellier.

In November, 1532, Rabelais was appointed physician-in-chief to the Hôtel Dieu at Lyons. Here he was in charge of 200 beds—some of them accommodating two or three people—and he saw all the patients daily. The hospital was the only one which admitted all types of case, from fevers to maternity, and he must have been kept busy. It is recorded that during his stay the mortality rate was reduced by 3%. Although Rabelais journeyed a good deal, and rarely settled anywhere for long, he practised medicine almost all his life.

Gargantua and *Pantagruel*, the books which won him immortality, are uninhibited—some critics have said coarse, though in the context of their times they do not seem to be unusually so. He advocated liberal doses of good food and drink, plenty of exercise, and adequate sleep. Nor was he concerned only with man's bodily welfare, for he believed laughter and the mental wellbeing it denotes to be his birthright and salvation. Many of Rabelais's descriptions overflow with physiological information—his picture, for instance, of the birth of Gargantua, miraculous and imaginative though it is. Gargantua's mother was given a drug which caused the child to leap from the womb "and entering the vena cava climb by the diaphragm above her shoulders (where that vein divides in two) and then taking the left branch issue from her left ear." If Rabelais contributed nothing of lasting value to the advancement of medicine—nothing to be compared with the achievements of his contemporaries Vesalius and Leonardo da Vinci—his legacy of laughter may rank as a great contribution to the wellbeing of man.

"An understanding of the scientific basis of good feeding should be part of the everyday knowledge of an educated community" according to the Ministry of Food's *Manual of Nutrition* (3rd edition, H.M.S.O., price 2s.). The book sets out to supply the necessary information. Much of it is elementary, but medical men called upon to advise on diets for varying age and occupational groups may find some useful tips in the sections on nutritional requirements and the composition of food (especially the valuable appendix A).

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Chlorophyll as a Deodorant

SIR,—From the letters written by Dr. W. Mitchell and Mr. L. Deadman (March 14, p. 621) it would appear that the alleged potency of chlorophyll and the chlorophyllins as deodorants varies so much that the experimentalist would be wise to use only preparations offered to the public by reputable firms. This is precisely what Dr. J. C. Brocklehurst did. He obtained his sodium copper chlorophyllin (so highly valued by Dr. Mitchell) from a chlorophyll manufacturer, and solution "C" was "a true sample of this substance as it is sold to the public" (March 21, p. 674). I have followed Dr. Brocklehurst's example by using a proprietary preparation of chlorophyll in tablet form called "amplex" for an "asparagus test" carried out on myself.

Critics of Dr. Brocklehurst's paper (*Journal*, March 7, p. 541) emphasized the need to allow chlorophyll an adequate period of time for deodorizing offensive gases and to ensure that there is an abundance of chlorophyll available. These exacting requirements are not mentioned on the label of the "amplex" containers, which merely says: "One tablet swallowed or dissolved in the mouth every morning for basic freshness all day." I decided, however, to leave nothing to chance, and took 100 tablets of "amplex" an hour after breakfast; and three and a half hours later I ate 40 more, making 140 in all. The tablets in the first batch were powdered and then washed down with sips of water; the second lot were chewed thoroughly and swallowed. After two and a half hours I ate a dozen asparagus tips (which also contained a considerable quantity of chlorophyll). In less than two hours my urine had the unmistakable and rather offensive smell which is a characteristic effect of eating asparagus. After six hours the odour was intense, and it persisted even in specimens voided on the following day. The timing of the dose of chlorophyll tablets makes no obvious difference. On one occasion I swallowed 100 tablets (powdered), and after seven hours I took another dose of 100 tablets, followed at once by a serving of asparagus. In less than two and a half hours the asparagus smell was apparent in the urine.

Such a test should not be regarded as a single instance of failure of chlorophyll as a deodorant. So long as there is a substantial quantity of chlorophyll in the alimentary canal, every occasion when an offensive urine is voided (say four or five times in 24 hours) must be considered as a separate test and as a separate instance of failure. I may add that during this particular experiment I noticed the taste and odour of asparagus in the occasional eructations that occurred. I have personal knowledge of ten such failures to add to the observations made by Dr. Brocklehurst on himself.

Dr. Brocklehurst says that "it would be helpful if a large number of doctors would themselves repeat this simple experiment." I agree, but we must not forget that the value of physiological and pharmacological experiments carried out on a solitary human subject may be of a very high order—as, for example, in the classic case of the observations on Alexis St. Martin and, more recently, in the studies on pain made by Kellgren and others. It is certainly not unreasonable to suggest that if chlorophyll is offered to the public as a deodorant its reputation must stand or fall by clinical trials on man—a subject which Dr. Mitchell "does not feel competent to discuss." It should be noted that there are special advantages in the asparagus test: it is simple to carry out, and the necessarily intermittent observations eliminate the fallacy of olfactory fatigue. Experimentalists will also take into account the fact that the malodorous substances are rapidly removed *in vitro* by treatment with a small quantity of activated carbon.

Dr. Mitchell speaks as an expert of the deodorant effect of sodium copper chlorophyllin in a chemical plant used for the distillation of garlic oil. This is interesting and doubtless important in the pharmaceutical industry, but it does not follow that the observations must necessarily have any clinical application. A description of the technical procedure which Dr. Mitchell mentions might enable clinicians to determine whether the process could be applied to the practice of medicine. Dr. Mitchell has suggested that chlorophyll "may catalyse oxidation of odorous material, perhaps by forming a loose combination with oxygen and parting with the latter at the sites of action."[1] But this hypothesis was destroyed by Kohler *et al.*,[2] who reported that chlorophyll is not absorbed from the gastro-intestinal tract. This disposes of any suggestion that oral medication with chlorophyll can abolish the fetor of, say, bronchiectasis or sinusitis.

Dr. Mitchell promises to produce evidence of the effectiveness of chlorophyll preparations in deodorizing benzyl mercaptan. This will be awaited with interest; but his experiments will be much more significant to clinicians if he will perform his tests with methyl mercaptan, which is known to occur in the human bowel. I therefore suggest that he should use methyl mercaptan. This will make it possible to compare his results with those of Dr. Brocklehurst and other workers. Further, there are fallacies attending the use of benzyl mercaptan for this purpose which do not apply to methyl mercaptan.

Mr. B. E. Chanell (March 14, p. 622) gives the names of two substances not contained in "airwick." Would he care to tell the medical profession the names of the constituents for which a deodorant action is claimed? Is chlorophyll one of them? Even more important, will he be good enough to explain how this preparation acts—if it acts at all? Is it seriously suggested that chlorophyll is dispersed through the atmosphere of a room, or does the air obligingly gravitate to the tiny impregnated wick and filter itself so rapidly that a few thousand cubic feet of air are dealt with in as many minutes?—I am, etc.,

Glasgow. STANLEY ALSTEAD.

REFERENCES

[1] *Retail Chemist*, 1952, **23**, 27, 65.
[2] *J. biol. Chem.*, 1939, **128**, 501.

SIR,—Your *Journal* is to be congratulated upon the article by Dr. J. C. Brocklehurst (March 7, p. 541) and upon its stand in connexion with it. I have read with interest the reactions to the article as conveyed by the *New York Times*.

I agree with Dr. Brocklehurst that the responsibility for demonstrating the effectiveness of chlorophyll or of its derivatives lies with the proponents of its use. In this connexion, the manufacturers of chlorophyll derivatives have themselves repeatedly failed to define their materials adequately. Most of the commercial materials now on the market consist of 50–75% alfalfa extractives other than the green pigments derived from chlorophyll. The demonstration that such an impure material has any given property has nothing whatsoever to do with the proposition that this property is inherent in the green pigment fraction of the material used. Since alfalfa oils are commonly left in the extracts used, it is incumbent upon the manufacturers to prove that any "deodorant" properties which the nose may detect are not, in fact, due to a masking of the undesired odour with alfalfa oil.—I am, etc.,

Baltimore, Maryland, U.S.A. ALSOPH H. CORWIN.

SIR,—Taking note of your evidence that chlorophyll preparations have no, or very little, deodorant action (March 7, p. 554), I would like to state that we have used the water-soluble, copper-treated chlorophyll "J. J.," in low concentration, soaked into one layer of gauze in between dressings for foul-smelling carcinomas and ulcerated legs, etc., and the result was quite remarkable. One demonstration was given to the nursing staff on a septic, gangrenous leg which through its intense foul smell was of annoyance to other patients. A piece of such gauze soaked with chlorophyll solution was dropped over the leg, and the smell quite dramatically disappeared. As long as treated in this way, no smell was present in the ward. A daily, relatively short medical inspection which confirmed this could hardly be long enough to render the olfactory nerve endings less capable of detection. Moreover, no crotonaldehyde or other substance than above was used. After many experiments this was the first time we were able to combat satisfactorily smells which arise only too frequently in large wards with chronic sick and at times create a problem. It should be said that chlorophyll does not diminish all smells, and not all chlorophyll preparations, pure or otherwise, have this

effect. Its action is undoubtedly selective, and I feel that in view of the results obtained here, not only as described but also in other forms, the experience of other users may be of interest.—I am, etc.,

Birmingham, 18. R. S. HOLZER.

SIR,—With reference to the annotation (March 7, p. 554) on the subject of chlorophyll, what most of us want to know is not whether an experiment conducted with elaborate apparatus on purified chemical substances yields a positive result, but whether ordinary people, using their noses in an ordinary way, can detect a deodorizing action in naturally occurring evil-smelling mixtures. It is quite untrue to suppose that such experiments cannot give conclusive results, for nowadays statistical design and experimental methods have been developed for just this kind of case. Attempts to eliminate the subjective element are apt to result in pointless experiments, but it is also true that many other experiments have been reported in which the proper precautions have been ignored and are therefore also nearly valueless.

We have carried out experiments reported more fully elsewhere (*Pharm. J.*, 1953, **170**, 209) in which 139 people were used as testers with precautions in design and analysis of results which we think exclude bias. We conclude that chlorophyll on cotton pads does reduce the odour of decomposing blood, the probability of our results arising by chance being less than one in 2,000 million.—We are, etc.,

D. MAXWELL BRYCE.
Barnet. R. MAXWELL SAVAGE.

Psychosomatic Medicine

SIR,—Most of your readers will have read with profound interest Dr. R. R. Bomford's paper on this subject (*Journal*, March 21, p. 633) and been grateful for the refreshing lucidity with which it was phrased. Most of them would surely agree, too, that in every consultation it is a body–mind something with which doctors have to deal—Dr. Bomford calls it a unity. But there are some of us, like Henry Head, who have never been able to persuade ourselves that there are any "diseases" of mind *qua* mind. The "diseases" are all of tissue, though mind can deeply affect them and is in turn—in its individual terrestrial expression (behaviour)—deeply affected by them. But the things that happen, or can be made to happen, to the individual mind itself, such as the development of tissue-influencing courage and equanimity, must occur, it would seem to us, in some non-material dimension. St. Paul's Cathedral, for example, was once a thought. The thought was as real as the cathedral. But where exactly was it after the moment of its birth? Was it occupying space inside the skull of Christopher Wren? When, as part of his mind, it accompanied him through the years on his daily journeys, was it indeed geographically occupying space anywhere? If mind is only just another aspect of matter, can matter—always occupying space—have an *integral* part or aspect *not* occupying space? It is because we find it so hard to believe this that we should have preferred, I think, to use the word tenancy rather than unity—though always prepared, I hope, to be shattered by our philosophical superiors.—I am, etc.,

Easton Royal, Wilts. H. H. BASHFORD.

Blackwater Fever

SIR,—The study reported by Lieutenant-Colonel Inder Singh (*Journal*, March 14, p. 598) is of considerable interest. We consider it unfortunate, however, that the term blackwater fever should have been used in the title of this paper as there is no incontrovertible evidence that this was the correct diagnosis.

An essential characteristic of blackwater fever is intravascular haemolysis, an occurrence which may be recognized by the presence of methaemalbumin in the circulating plasma, an increase in the serum bilirubin, and clinically by jaundice. In the cases reported there is no mention of jaundice, while no estimates were made of plasma methaemalbumin. Serum bilirubin was estimated in one case and was within the normal range. In that case, tests carried out on serum and urine for haemoglobin and methaemoglobin were negative; in the other oxyhaemoglobin and methaemoglobin were found in the serum, and haemoglobin —presumably oxyhaemoglobin—in the urine. Blackwater fever is not the sole possible cause of the findings in the latter case, and is contraindicated by those in the former. Without further information the diagnosis must be regarded as unproved.—We are, etc.,

P. C. C. GARNHAM.
London, N.W.1. A. W. WOODRUFF.

Smoking and Lung Cancer

SIR,—If one may descend for a moment from the clouds of speculation and somatomorphology to the more pedestrian subject of tobacco smoke, I should like to point out an aspect of aetiology which I have not so far seen mentioned.

Theories of carcinogenesis have had to be revised in the light of recent work by Berenblum and Shubik.[1] These workers have presented evidence that the process of carcinogenesis may be divided into two distinct stages. There is an initial phase when a carcinogen, and only a carcinogen, causes a specific cell change which may remain latent. Actual tumour formation can only be brought about by further application of either a carcinogen *or a non-specific irritant* which acts as a co-carcinogen. Many such irritants are now known which, though incapable of causing carcinoma by themselves, are able to do so when applied to a tissue previously exposed—even only on a single occasion —to a carcinogen. In experimental work the total tumour incidence is found to depend on the strength of the carcinogenic "initiator," and the latent period before the appearance of a tumour depends on the time and intensity of subsequent applications of a co-carcinogenic "promoter."

We know that the atmosphere of cities, and road dust, contain benzpyrene and probably other carcinogens derived, no doubt, from tarred roads, coal smoke, and soot, etc. Here are known sources of an initiating carcinogen which must often be inhaled. Continued exposure to these carcinogens can by itself lead to tumour development, as they also possess a promoting action. But it may well be that other irritant substances not carcinogenic in themselves could, if inhaled regularly over long periods, have a powerful co-carcinogenic promoting action on cells already transformed by the carcinogen into latent tumour cells.

It would seem worth investigating whether tobacco smoke contains any such co-carcinogenic irritants. If it were found to do so, it would explain the apparent "carcinogenic" significance of cigarette smoking in the absence of any recognized carcinogen (of the initiating type) in tobacco smoke. It might then even be possible to remove by suitable filters the noxious agent from tobacco smoke, to the relief and joy of nicotinophils.—I am, etc.,

Swansea. D. K. SAMBROOK.

REFERENCE

[1] *Brit. J. Cancer*, 1947, **1**, 379 and 383.

SIR,—It may be a good thing for the patients to stop smoking, but if the doctors were to do so what would become of the statisticians' experiment?—I am, etc.,

Hove. CONSTANCE M. OTTLEY.

Cancer Education

SIR,—The circular sent to general practitioners by the British Empire Cancer Campaign has just been brought to our notice.

It might interest your readers to know that the Central Council for Health Education has also been considering for some time the desirability of cancer education, and has conducted experimental educational campaigns in about a dozen areas, both rural and urban. In each case the mayor

or chairman of the health committee invited all interested parties from the medical side and representatives of local lay organizations to a meeting at which there was a talk by a cancer authority on the present position of cancer and its treatment. Discussion then ensued, and the audience were asked whether they considered it a suitable subject on which to call meetings of the organizations they represented. In nearly all cases it was resolved to set up a cancer education committee, and these are now functioning under varying constitutions in many areas. The reaction of the representatives of general practitioners varied from area to area, but with one or two exceptions was favourable, mainly because they were able to see the interest of the public in the subject and their level-headed appreciation of the issues, and were able to satisfy themselves that the type of education proposed was not such as to cause alarm or hold out extravagant promises.

Reading the British Empire Cancer Campaign questionary, it seems to us that many practitioners may answer "No," mainly because they have frequent experience of cancerphobes, and have not had the opportunity of taking part in such a conference. We hope very much that this questionary, which seems prejudiced in favour of the answer "No," will only be interpreted as a very slender piece of evidence.—We are, etc.,

Central Council for Health Education, London, W.C.1. S. G. DEAN. JOHN BURTON.

Intravenous Iron

SIR,—I have read with considerable interest the article on "Toxic Reactions due to Intravenous Iron" (January 3, p. 21) just received. We work in an area where there is a 95% infestation with hookworm, and patients with haemoglobin levels of 15–20% (Sahli) are admitted almost daily. There is no blood available for transfusion, and it is a matter of some urgency to raise the haemoglobin level in the blood, particularly in cases of advanced pregnancy, where this degree of anaemia is usually associated with gross oedema and a dilated heart. Although we are only a 50-bed hospital, we give literally hundreds of intravenous-iron injections a year. The preparation available out here is "iviron," and we usually give 5 ml. (100 mg. of iron) on admission and 10 ml. (200 mg. of iron) on alternate days for three doses, which usually brings the haemoglobin to 50% or so.

It would be interesting to know the percentage incidence of toxic reactions in England. We have never encountered any here except a rise of temperature up to 102° F. (38.9° C.) on the day of injection. I only hope these are not "famous last words."—I am, etc.,

Narsapur, India. BETTY D. HOLT.

Frustration in the Hospitals

SIR,—Some may be indignant and surprised at the interference of the Minister of Health with the details of management of the great teaching hospitals of London. May I express my opinion that they need be neither surprised nor indignant? The "frustration" that has happened is strictly in sequence and conformity with the previous actions of the Minister, whatever his political colour. In my presidential address to the Surrey Branch of the British Medical Association last June, I drew attention to the vast progress made in medicine by the initiative of the individual doctor since the times of Hippocrates of Kos over 2,000 years ago. It was exemplified in the last 300 years in England by Harvey's discovery of the circulation of the blood, Jenner's discovery of vaccination for the prevention of smallpox, Lister's discovery of antiseptics, Ross's discovery of the transmission of malaria by the mosquito, and Bruce's discovery of the transmission of Malta fever by the goat and of sleeping sickness and allied diseases by the tsetse fly, to mention but a few. When medicine became the "plaything of politics" under the so-called National Health Scheme, it was, as Bertrand Russell pointed out, to invite interference with the general practitioner and also, as admitted by the late medical adviser to the Ministry of Health,[1] to make his work more difficult. The confiscation of the Kingston Hospital, in spite of the strongest local protest supported by the medical profession throughout the country, shows that public opinion counts for less than nothing in the mind of the case-hardened official. What happened in Kingston is only a forerunner of what is happening in the London hospitals to-day. Only by removing all medical services from politicians and Civil Servants, the former of whom just catch votes, and the latter work by rule, can a satisfactory medical service become possible.

What are now required are English, Welsh, and Scots corporations elected by the medical profession, not nominated by the Minister. They should be charged with organizing and operating the best possible medical services with the money available. The Minister of Health would then be free to study the cost, with the Government co-operating, of removing the unhealthy influences, which I set out in my address and copied from the statement of the British Medical Association, affecting good food, good houses, clean air, etc., which the medical profession is not competent to carry out. Guided by the medical profession, the Minister would have abundant work to do and he would provide the global sum required.—I am, etc.,

Peaslake, Surrey. MALCOLM WATSON.

REFERENCE

[1] *Supplement*, 1951, 1, 89.

Handwriting and Personality

SIR,—The medical profession should be grateful to you that you have given so objective and lively an account of "Handwriting and Personality" (*Journal*, March 14, p. 607). As I have been a student of handwriting for over 30 years (and a psychiatrist), I hope you will allow me to write about some points regarding graphology.

First, there are many more than two camps of graphologists. In my opinion, and according to my experience, the schools following Dr. Ludwig Klages (Germany), and especially Robert Saudek (Czechoslovakia), are the only ones which should be taken very seriously. Any serious graphologist considers not only single signs, such as peculiar characters, t-bars, i-dots, etc., but the handwriting as an entity. There is the size of the characters, the spacing both vertical and horizontal, margins, pressure, speed, signature, and some more projected features of personality. The one and only difficulty lies in that the interpretation of these signs is not uniform, although many graphologists have arrived at identical interpretation and evaluation of the main features. After all, science is based, in general, on observation, comparison, and relevant conclusion. These principles are applied in serious graphology, and I am convinced that the fundamentals of personality can be assessed by means of graphological analysis.—I am, etc.,

Prudhoe-on-Tyne. A. D. HELLER.

Lung Resection for Pulmonary Tuberculosis

SIR,—Mr. F. Ronald Edwards claims (March 7, p. 561) that "resection is not carried out through an area of active tuberculous endobronchitis." I wonder what evidence Mr. Edwards may have to support this claim. In an investigation carried out on behalf of the British Tuberculosis Association[1] I found active tuberculous bronchitis at the site of amputation in no less than 91 of 95 specimens. These specimens were limited to those cases in which the proposed site of amputation was within range of bronchoscopic vision, and in all cases the bronchus was reported upon before operation. In 56 cases no abnormality was detected. In the remaining 39 cases in which some abnormality was reported this usually took the form of slight redness or slight oedema. Clearly the value of a negative report by the bronchoscopist in suspected cases of tuberculous bronchitis is of very limited value. This is largely due to the fact, well known to pathologists though often ignored by clinicians, that quite serious bronchial disease is often covered by intact and normal epithelium. These figures go a long way towards solving the question posed

by Dr. F. H. Young (*Journal*, February 7, p. 287): "Are we paying too little attention to minor bronchoscopic findings?" It should also be mentioned that the material for the British Tuberculosis Association's investigation came from six different hospitals.

Mr. Edwards asks for a fuller explanation of the statement that "pulmonary tuberculosis is a generalized disease." The following points may assist him: (1) In the majority of resected specimens there is evidence of tuberculous endobronchitis at the site of surgical amputation. Similar lesions may be found very frequently in the normal parts of resected lobes and lungs. These lesions are frequently separated from frank, obvious tuberculous lesions by quite wide areas of lung and bronchus which are normal both to the naked eye and on histological examination. The exact significance of these lesions is still unknown, but nevertheless they are clear evidence of a generalized disease. (2) In the vast majority of a very large number of surgical specimens from cases of pulmonary tuberculosis the pathological areas have been found to be more extensive than was expected from the critical study of a long series of radiographs. (3) Where a limited resection had been intended but has, at operation, been found impossible and the "sacrifice of healthy lung tissue resorted to," the healthy lung tissue has almost without exception been found to contain macroscopic foci of either pneumonic or bronchial tuberculosis.

The fact that these lesions may be impossible to visualize in radiographs, and difficult to find in the specimen unless adequately searched for, does not constitute a licence to ignore them. On the contrary, they provide a challenge to the clinician, the radiologist, and the pathologist to co-operate in solving the problem of their significance.—I am, etc.,

London, S.W.3. J. W. CLEGG.

REFERENCE

1 *Tubercle*, 1953, 34, 74.

Tuberculosis Case-finding

SIR,—My colleagues and I are grateful to Dr. H. G. Calwell (February 14, p. 404) for drawing attention to the omission in our article (January 10, p. 64) of any reference to the examination of the teachers in the infant schools where the children were tuberculin-tested. No sort of attempt was made to examine the teachers. We entirely agree with Dr. Calwell that schoolteachers are a most important group who should be routinely examined, but such a project raises a number of various issues which we rather sought to avoid in the present investigation. We decided before the investigation began that if in any one school or class an unusually high proportion of tuberculin-positive reactors appeared our first measure would be to *x*-ray all the teachers concerned. However, that did not arise. Analysis of our material showed very little difference in the proportion of positive reactors in each age group from school to school in the different parts of the town. There was a slight, but not significant, suggestion that schools serving new housing estates in particular had a lower proportion of positive reactors.

We entirely agree with Dr. Calwell that the regular *x*-ray examination of schoolteachers is a most desirable, and reasonable, measure for an education authority to adopt.—I am, etc.,

Bournemouth. W. H. TATTERSALL.

Compressive Lesions of the External Popliteal Nerve

SIR,—I read with interest the article by Drs. Hugh Garland and Doreen Moorhouse on "Compressive Lesions of the External Popliteal Nerve" (*Journal*, December 27, 1952, p. 1373). About the time this article appeared I was consulted by a European male, aged 54, who had been suffering from foot-drop on the left side for one week. There were no paraesthesiae. He was a heavy drinker and had suffered at one time from delirium tremens. He attributed the paralysis to the wearing of puttees.

On examination there was a complete paralysis of the muscles supplied by the anterior tibial nerve; the peronei were normal and there was no anaesthesia. Palpation of the leg revealed a softish sausage-shaped swelling 3 in. (7.5 cm.) long, the upper border of which was 1½ in. (3.7 cm.) below the neck of the fibula. It was not easily palpable, as it was beneath the deep fascia and his legs were rather fat. The swelling was transilluminated and evidently contained clear fluid. There was nothing abnormal palpable at the neck of the fibula. Ten days later the nerve was explored. Beneath it, as it crossed the neck of the fibula, was a small ganglion about the size of a pea, and this was removed. The swelling lower down consisted of a chain of similar cysts arising in the septum between the peronei and the soleus. These were also excised. The day after the operation there was substantial recovery in the affected muscles and their power was normal in two weeks.

The interest in this case lies in the nature of the compressing agent, which was not palpable clinically; the fact that, though the nerve was involved before its bifurcation, the muscles of the anterior compartment only were affected—one would, of course, expect motor nerves to be more susceptible than sensory; and the rapid recovery after operation. Had the other ganglia not been palpable one would presumably have treated the case conservatively.—I am, etc.,

Nairobi. J. A. S. GREEN.

Fatal Anaphylactic and Anaphylactic-like Reactions

SIR,—With reference to the report by Mr. G. S. Ramsay (*Journal*, February 21, p. 439) of a death following intravenous administration of iodoxyl, and the letter of Dr. H. J. Barnes (March 14, p. 618), I wish to add the following comments on the pathogenesis of fatal anaphylactic and anaphylactic-like reactions. Solutions or suspensions of any substance whose molecules possess a highly active surface-acting force are liable to precipitate an anaphylactic-like response if given intravenously. These molecules initiate a rapid and chaotic proteolysis by a physico-chemical mechanism, resulting in the liberation of toxins identical with those acting in anaphylactic shock (Godlowski[1]). The activated tryptic enzymes can be again inactivated by heparin, which, if given in high dosage, forms a heparin-tryptic enzyme compound deprived of hydrolytic potency (Rocha a Silva[2]). Adrenaline, a potent agent in combating the hypotension in the anaphylactic reaction, cannot avert the fatal issue of these reactions, because it does not influence the basic pathogenetic phenomenon of toxic proteolysis. The rational treatment of anaphylactic and anaphylactic-like reactions in men is intravenous infusion of adrenaline (Godlowski[3]), with the addition of heparin in high dosage (Godlowski[4]) and any potent antihistaminic compound, all in glucose saline solution. Problems of anaphylactic and anaphylactic-like responses are dealt with at length elsewhere (Godlowski[5]).—I am, etc.,

Edinburgh. Z. Z. GODLOWSKI.

REFERENCES

1 Edinburgh University, Ph.D. thesis, 1952.
2 *Histamina e anaphylaxia*, 1946. Edigraf, Sao Paolo.
3 *British Medical Journal*, 1946, 1, 717.
4 *J. Endocr.*, 1952, 8, 102.
5 *Enzymatic Concept of Anaphylaxis and Allergy*, in press. E. and S. Livingstone, Edinburgh.

Modern Treatment

SIR,—Sir Robert Hutchison's letter on modern treatment (March 21, p. 671) brings back the memory of another great teacher and colleague of Sir Robert's at the London Hospital—the late Mr. Russell Howard.

Russell Howard, like Sir Robert, did not approve of the "prevailing fashion of obscuring things by calling them by their initial letters." In fact, he abhorred this type of abbreviation, and when a student asked him: "What about N.A.B. in this case, Sir?" he replied with a characteristic smile: "I will answer you in your own coinage, N.B.G."—I am, etc.,

London, W.1. MICHAEL SMYTH.

SIR,—I read Sir Robert Hutchison's letter (March 21, p. 671) with interest and no little comfort. I am one of those to whom the majority of articles in the *Journal* of

to-day mean little or nothing, and it is a comfort to know that I am, in this, in such good company. Many of the titles to such articles do little for me beyond recalling the lines of Goldsmith describing the village schoolmaster:

"While words of learned length, and thundering sound,
"Amazed the gaping rustics ranged around."

In the last line put in the words "general medical practitioner," or, to be in the fashion, G.M.P., and so add to the long list of letters in place of words, and thus still further confuse and exasperate the reader.—I am, etc.,

Watford. THOMAS FENTEM.

SIR,—I am reassured to learn that such a distinguished physician as Sir Robert Hutchison (March 21, p. 671) often finds, as I do, that many of the articles in the *Journal* mean nothing to him. I suppose these articles and the work that goes into them may be expected to contribute to medicine in the future, though it is sometimes difficult to see just how and why.

The ultra-scientific spirit in medicine seems now to have got out of control and is perhaps a reflection of our time. Younger members of the rank and file cannot escape these influences. Perhaps it represents a *trahison des clercs* in the medical profession—as doctors are taught so they will approach clinical medicine.

Dr. R. R. Bomford's Bradshaw Lecture (March 21, p. 633) on "Changing Concepts of Health and Disease" exemplifies the critical and thoughtful leavening and corrective we need to counteract mere "scientism." A welcome addition to the otherwise disheartening mountain of textbooks on the scientific aspects of medicine would be a textbook on such features of the art of medicine as these. It would benefit those of us suffering from an excess of mechanics and super-science and could well be written by a man of the experience of Sir Robert Hutchison.—I am, etc.,

Bridgend, Glam. H. M. FLANAGAN.

An Unusual Case of Chickenpox

SIR,—A 6-year-old schoolboy received a boosting dose (0.2 ml.) of A.P.T. by deep intramuscular injection into the left arm, above the insertion of the deltoid. Next day he complained of stiffness and pain in the arm, which was red and slightly swollen around the site of injection. On the fourth day the arm was red, hot, and swollen from the shoulder to the elbow, yet there was little constitutional disturbance. Each day thereafter a steady improvement was noted. On the ninth day, however, a crop of vesicles appeared on the left arm concentrated around the site of inoculation. Examination of the rest of the body surface, and of the mouth, proved negative. Next day (the tenth day) the lateral surface of the arm was heavily studded with vesicles, so numerous as to be almost coalescent, while a few vesicles were found on the scalp, chest, abdomen, and in the groins, justifying a diagnosis of chickenpox. There had been numerous cases of chickenpox among pupils of the school which this boy attended.

It is presumed that this boy received his booster dose of A.P.T. while actually incubating chickenpox. The selective action of the virus for an area where slight tissue damage and hyperaemia were present is well demonstrated.

My thanks are due to the general practitioner, Dr. E. R. L. Gregson, for his co-operation.—I am, etc.,

Kirkcaldy. JAMES A. PETRIE.

Advertising

SIR,—The recent flood disaster has given to all men of good will a great opportunity of eliminating waste in every department of expenditure. It seems that the world in general is going to go short of food in some five years' time, and we are all encouraged to take such steps as we can to increase our productivity against this imminent disaster. It has been stated officially that our share of the earth's surface is adequate, whereas the manpower to match it is deficient. Some of us are aware of serious waste in the use of valuable manpower in advertising to, and by, the medical profession. I presume my case can be multiplied by thousands. In a fortnight I received 18 circulars, two of them 7 in. by 9¼ in. Most of them are printed on expensive paper, nearly all of them are illustrated, and some of the illustrations appear to reflect in the mind of the advertiser some symbolical significance which does not readily jump to the eye. The amount spent in postage, once a valuable item in the Postmaster's returns, is now a source of understandable dissatisfaction on the part of the Post Office staff. This spate of advertising comes down to the competitive element in free distribution. I will be told by the professional advertisers that I do not understand the importance of building up and maintaining goodwill and good name. Perhaps this is so, but no one can get away from the fact that manpower is being wasted in producing and circularizing on a scale so vast.

I suggest that medical men should approach, in a conciliatory spirit, the Chancellor of the Exchequer, in the hope that he will put a stop to the overflowing waste-paper baskets of a profession which has already too much paper with which to cope.—I am, etc.,

Harrow. H. CRICHTON-MILLER.

Intravenous Barbiturates for Drunkenness

SIR,—I feel that certain points from Dr. A. H. Bartley's letter (January 17, p. 163) require further comment, since this method of treatment as described therein is potentially dangerous, the more so as it is a method which by its very simplicity may well appeal to the harassed casualty officer or other hospital resident, particularly if newly qualified, when confronted with patients who are violent and disorientated in their drunkenness.

The quelling of a drunken patient by intravenous thiopentone, unless preceded by thorough stomach wash-out, contravenes one of the most important rules regarding the administration of an intravenous anaesthetic—namely, that thiopentone must never be given to a patient where a full stomach is suspected. The well-recognized phenomenon of "silent regurgitation" of gastric contents up the oesophagus and their inhalation into the trachea constitutes a very real risk if thiopentone is used in such cases. Even if no inhalation of gastric contents occurs, the risk of severe glottic spasm is a grave hazard to some patients, particularly the elderly hypertensives, where the subsequent strain imposed upon the myocardium is badly tolerated.

Apart from the increased likelihood of local venous thrombosis following the use of a 10% solution, as Dr. Bartley suggests, the risks mentioned are in no way diminished, for it is then more difficult to inject a given dose of the drug as slowly as if the customary 5% solution were used. Assuming that the stomach is empty, and even though the injection of a mere "sleep dose" is contemplated, some means of positive-pressure oxygen administration should be immediately at hand. For those interested, the excellent article by Drs. H. J. V. Morton and W. D. Wylie (*Anaesthesia*, 1951, **6**, 190) on anaesthetic deaths due to regurgitation or vomiting should be read.

In view of the points mentioned, the writer feels that a far safer, if less dramatic, method of calming the obstreperous drunk is the intramuscular injection of 10 to 20 ml. of paraldehyde. Alternatively, subemetic doses of apomorphine have been found effective by some clinicians.—I am, etc.,

London, W.2. PETER NOBES.

Polypharmacy

SIR,—It is with regret that I note in your columns an advertisement for a new haematinic which recalls the palmy days of polypharmacy; it is said that each capsule of this preparation contains 192 mg. ferrous sulphate, 10 micrograms vitamin B_{12}, 0.85 mg. folic acid, 50 mg. ascorbic acid, 100 mg. powdered hogs' stomach, and 350 mg. of an insoluble liver fraction; and it is recommended as "the greatest step forward yet made in the treatment of the

common anaemia," and "invaluable in the treatment of nutritional hypochromic anaemia, post-infectious anaemia, the megaloblastic anaemias of pregnancy, infancy, pellagra and sprue and allied dyscrasias."

Whatever may be the situation in the United States, this polypharmacy is not needed in Britain. The megaloblastic anaemias of pregnancy, infancy, peliagra, and sprue are so rare that a full-scale investigation is needed before any such diagnosis can be accepted; treatment may then be with folic acid, vitamin B_{12} and ascorbic acid, nicotinic acid, etc., whichever is indicated. Nutritional hypochromic anaemia—an elegant term for iron deficiency—can be treated quite efficiently by simple iron salts or by injection of saccharated iron hydroxide.

Further, such blunderbuss preparations are dangerous, because they prevent accurate diagnosis. I was asked recently to study an anaemic patient who had received iron salts, folic acid, liver extract (parenteral and oral), vitamin B_{12}, and a mixture of other B vitamins. This treatment had effectually destroyed the clues on which I depend, and I could not help the patient. Another patient, referred to a colleague for diagnosis of a suspected pernicious anaemia, received oral and parenteral liver extract only 24 hours before reference to hospital for investigation—making the diagnosis unnecessarily difficult. No one can exaggerate the importance of diagnosis in anaemia, or the difficulty of establishing it after treatment has started. In more than nine cases out of ten a simple history and simple laboratory tests suffice to establish the diagnosis—and laboratory tests are becoming available to more and more practitioners.

One must conclude that the manufacturers of this new confection are hoping to divert a larger proportion of the nation's drug bill into their own pockets. This is a lawful—and perhaps even a commendable—aim: but the money available for the Health Service is limited, and the cost of curing a patient with the new remedy is likely to exceed that of curing him with some simpler and less elegant preparation. It is difficult to escape the conclusion that to order so elegant a preparation is against the best interests of patients and of the country.

Such sentiments are spreading among the younger consultants and their registrars. Our task to-day is to restore to health (and work) as many patients as possible, and to do this with the minimum of expense. Recently it was pointed out that about £240,000 has been wasted by ordering a proprietary preparation in place of its official equivalent. When public moneys are wasted on this scale those who encourage such expenditure are challenging the Government of the day, one of whose chief tasks is to secure value for money. The introduction of unnecessary, high-priced polypharmaceutical mixtures encourages waste of public money and must bring forward the day when practitioners are allowed to prescribe only from a standard formulary and manufacturers will have to secure a licence to use a proprietary name for their preparations. The introduction of such mixtures is against the best interests of the medical profession and of the pharmaceutical industry.—I am, etc.,

London, N.W.10. GEORGE DISCOMBE.

Treatment of Impetigo

SIR,—In the reply to the question on the treatment of impetigo ("Any Questions?" March 14, p. 631) your expert wisely stresses the undesirability of interference with lesions. But it is surely impossible to avoid interference if pastes or creams are used, as recommended. It is my experience that a foolproof method of treatment is that of eau d'Alibour (lot. cupri et zinci sulph. *N.F.*) with 50% spirit, applied every three or four hours in the form of a spray. Exudation ceases after 24–48 hours, and within a few days the crusts will have separated and will drop off spontaneously. The de Vilbiss spray or similar apparatus could presumably be loaned to the patient on the payment of a returnable deposit.—I am, etc.,

Portsmouth. RONALD SCUTT.

Operative Treatment of Hallux Valgus and Rigidus

SIR,—I would like to support Mr. N. Ross Smith (January 31, p. 274) in his contention that arthrodesis of the metatarso-phalangeal joint is the operation of choice for hallux rigidus and valgus. Whilst agreeing with Professor Bryan McFarland (p. 275) and Mr. J. M. P. Clark (January 17, p. 162) that Keller's operation and Mayo's operation are both capable of producing good results in a high proportion of cases, there is no doubt that occasionally they may both produce a very bad result. The bad results are invariably due to interference with the head of the metatarsal, weakening the transverse arch and aggravating still further the well-known disabilities produced by a short metatarsal.

I have not yet seen a single bad result following arthrodesis of the metatarso-phalangeal joint, but would like to suggest the following variation in technique, which was suggested and introduced to me by Mr. J. B. Leather and is what he appropriately called a "two-stage Girdlestone." First, the metatarso-phalangeal joint is arthrodesed in the straight position, by simply denuding the articular surfaces of cartilage, leaving a smooth concave base of proximal phalanx and a smooth convex head of metatarsal. The foot and great toe are then immobilized in a plaster case, the metatarsal arch being well moulded. One month later, the plaster is removed, and the distal half of the proximal phalanx is excised extra-periosteally in order to restore dorsiflexion of the toe. Two to three weeks later the patient has a good strong foot and no physiotherapy is usually needed. In elderly patients not wishing to engage in strenuous activities, I modify the technique in leaving out the second stage, but anticipating this by arthrodesing the metatarso-phalangeal joint in 30 degrees dorsiflexion.

Finally, I would make a plea for careful selection of patients. If the symptoms are essentially due to the bunion and exostosis, provided the joint shows no evidence of arthritis, then simple removal of the exostosis is all that is necessary; the valgus deformity in itself is not an indication for interference with the joint, but arthritis is.—I am, etc.,

Wolverhampton. J. H. KIRKHAM.

Treatment of Threadworms

SIR,—Dr. W. Ivon Hayes's inquiry (February 28, p. 510) about the relation of the incidence of threadworm infection to the consumption of meat is a stimulating one, but it is probably unanswerable. Unless surveys are made by National Institute of Health (N.I.H.) swab, pestle, adhesive cellulose tape, or one of the other reliable methods (Watson and Mac Keith[1]) they are of little value. Most infected people have no symptoms, and clinical impressions of incidence cannot be trusted. Unfortunately the only surveys in this country are of 1941 and 1946 (Young[2] and Mac Keith and Watson,[3] and a fuller report to be published). Furthermore, is it not true that with rationing the consumption of protein has changed more in its distribution than in its total, the present consumption being 90% of pre-war?

The suggestion made by Dr. Hayes may well be correct, but I doubt whether it is true that children with oxyuriasis are more often "hungry, especially for sweets and sugar." It was evident from asking the mothers of a large number of children that the incidence of bulimia, of nail-biting, and of nose-picking was not higher in the infected ones. The only symptoms attributable to oxyuriasis were perianal itchiness and consequent disturbed sleep and fatigue.

Although the generally better hygienic habits of adults may account for their relative freedom, there is evidence (Schüffner and Swellengrebel[4]) that infection may occur per anum, vitiating the benefits of hand-washing before meals. A chemical difference in bowel contents is perhaps the reason. What is the incidence of oxyuriasis in the well (protein) fed children and adults of Melbourne?—I am, etc.,

London, S.E.1. RONALD MAC KEITH.

REFERENCES
1 *Arch. Dis. Childh.*, 1952, 27, 526.
2 *Proc. roy. Soc. Med.*, 1941-2, 35, 684.
3 *Practitioner*, 1948, 160, 264.
4 *J. Parasit.*, 1949. 35, 138

Intercourse after Syphilis

SIR,—When asked in the first place to answer this question I realized that the period advised for resumption of intercourse after treatment would arouse some critical comment.

Colonel L. W. Harrison (February 28, p. 510) quotes in full the statement made by Klauder in the discussion following the

paper by Pariser,[1] but the dermatologists and syphilologists of Philadelphia who followed this work very closely testify to the fact that no spirochaetes were found in the semen unless there were active lesions in the genital tract. Stokes and his collaborators in the standard textbook on syphilis[2] state: "The source of spirochaetes in the semen seems to be the real question at issue. . . . This [the work of Pariser] would seem to set at rest, if confirmed, the belief that there is a rest form of *Spirochaeta pallida* capable of being carried in the sperm or semen and capable of transmitting the disease to the ovum instead of to the foetus through the mother. Kemp has established for late syphilis the same principle which Pariser established for early syphilis."

None of the correspondents has presented any new evidence to support his point of view, and a great deal of their thinking is based on the pre-penicillin therapy of syphilis when the time required to effect a cure was much longer than it is now. Penicillin has revolutionized the treatment of syphilis, and the writer has used it in a large number of cases with no relapses and only two reinfections. It may also be noted that the incidence of the disease, especially in this country, is now extremely low, and before many years have elapsed it may well be as rare as rickets or chlorosis.

The available scientific evidence supports the overwhelming evidence of practical experience that intercourse without protection is permissible six months after completion of treatment.—I am, etc.,

"YOUR EXPERT."

REFERENCES

[1] *J. invest. Derm.*, 1942, **5**, 311.
[2] *Modern Clinical Syphilology*, 1944. Philadelphia.

SIR,—The correspondence recently published in the *Journal* suggests that this is a difficult question. I think the answer depends on whether we consider the problem from a theoretical point of view or in the light of ordinary practice.

Theoretically, as long as we have no test of cure that is 100% reliable, any intercourse between married or unmarried people is to be forbidden. In ordinary practice, this sort of prohibition would not be complied with, and it seems to me that it cannot be enforced, for the following reasons: (*a*) Experience has shown us that after using "modern" treatment (9 or 15 mega units penicillin, in France) no contaminated partner and no syphilitic newborn children have been seen, even if the patients do not wait for six months' negativity before resuming intercourse; (*b*) with such treatment we have not seen true relapse (reinfections and minute modifications of serological tests being disregarded, after a period of six months of negativity. We know one case only, a muscular gumma (?) in a tabetic patient (which is a rather uncommon case), the diagnosis of which could not be made from a biopsy. Rationally the contamination of partners or of babies remains still more unlikely than the occurrence of some late manifestation in the treated patient; and (*c*) disclosure of syphilis means a severe psychological shock to the patient and for a married couple. To forbid intercourse for years, because of a very slight risk, creates an obsession that syphilis is incurable and may wreck the marriage. Indeed, this possibility seems more dangerous to me than a contamination which could be treated very easily, and this social aspect deserves consideration.

The fact that a treponema can be present in a spermatozoon head (or rather stick to its surface) is a very interesting one, for it will support the hypothesis of foetus contamination by the father, without contamination of the mother. In any case, this is not relevant, for Finger and Landsteiner, Uhlenhuth, Bessemans, Levaditi, and Vaisman's experiences were drawn from non-treated people or animals with active syphilis.

I consider that we must be satisfied with your expert's answer, and allow intercourse after a six months' period of serological and C.S.F. negativity, especially when the usual serological tests are controlled by a treponemal immobilization test. However, in pregnancy, in order to prevent any possibility of trouble, I suggest that the mother be treated as follows: 9 mega units of procaine penicillin at the very beginning and 9 mega units near the end of pregnancy, when she has no more intercourse. When the husband's syphilis cannot be disclosed to his wife, a gynaecological excuse is easy to find.—I am, etc.,

L'Hôpital St. Lazare, Paris. P. DUREL.

Obituary

IRWIN MOORE, M.B., C.M.

Dr. Irwin Moore, who died at his home in Wimpole Street on March 23 at the age of 86, was almost the last of the older generation of British laryngologists, and was a link with the golden age of consulting practice in London, which ended in 1914. In earlier years he had made many important contributions to laryngology.

Dr. Irwin Moore's father, Dr. George Moore, of Hertford Street, London, had been a young assistant in Staffordshire until he was called, in the absence of his principal, to attend at Trentham the famous Duchess of Sutherland, who in her day ruled London society—Queen Victoria, attending some function at Stafford House, is reputed to have said, "I have come from my home to your palace." Dr. Moore was a handsome young man, to whom the Duchess took a fancy, telling him that if he would come to London she and her friends would support him, and he quickly built up an aristocratic practice in Mayfair.

Dr. George Moore's son, James Lennox Irwin Moore, was born in 1866, and was educated at Westminster School and Edinburgh University, where he graduated M.B., C.M. in 1893. After the usual house appointments at Edinburgh, he spent five years in general practice at Market Harborough, but in 1900 came to London to devote himself to laryngology. He became chief assistant in the throat department at King's College Hospital, and for a number of years was private assistant to Sir StClair Thomson. He was appointed honorary surgeon to the old London Throat Hospital in Great Portland Street, which amalgamated with the Throat Hospital, Golden Square, in 1914. Irwin Moore was never particularly happy about this amalgamation, and it was without regret that he left Golden Square, where he was honorary surgeon, to join the staff of the Metropolitan Ear, Nose and Throat Hospital in 1922 as senior assistant surgeon. He had been promised promotion to full surgeon after a short probation, but when after two or three years this did not eventuate he resigned. The committee of management were happy to assuage an old grievance in 1946, when he was appointed consulting surgeon to the hospital.

He was an energetic honorary secretary of the Section of Laryngology of the Royal Society of Medicine in 1919, and in the nineteen-twenties there was hardly a meeting of the Section where he did not show cases and never a volume of the *Journal of Laryngology* without one or more important articles from his pen. In 1925 he was vice-president of the Section of Laryngology and Otology of the B.M.A. at the Annual Meeting at Bath, where he showed an important collection of early endoscopic instruments. His contributions to the literature included articles on "Achalasia of the Oesophagus" (1918), "Angeiomata of the Larynx" (1921 and 1923), "Prolapse of the Laryngeal Ventricle" (1922), "Stenosis of the Larynx" (1923), "Cartilaginous Tumours of the Larynx" (1925), "An Historical Survey of Peroral Endoscopy" (1926), and "Oesophagectasia" (1927), all of them well illustrated and with copious bibliographies. He was one of the leading British pioneers of endoscopy, and invented ingenious instruments for use in bronchoscopy and oesophagoscopy, perhaps the most notable being his large-diameter

oesophagoscope and his useful cutting-shears. In 1921 he published a book entitled *Intrinsic Cancer of the Larynx and the Operation of Laryngo-fissure*, based on his experience "in performing or co-operating in over 50 cases of laryngo-fissure," and he was perhaps a little naïve in being surprised that Sir StClair Thomson was annoyed at the appearance of the book, of which he knew nothing until its publication, for most of the recorded cases were those at which Irwin Moore had assisted StClair Thomson, though Irwin Moore had designed a useful set of instruments for the operation. In 1928 he published a large volume entitled *Tonsils and Adenoids and their Diseases*, fully illustrated and with numerous references; in this he laid much emphasis on the value of treating chronic tonsillitis with an escharotic paste, "London paste," the formula of which he had found in Morell Mackenzie's classical textbook on diseases of the throat, and with which he treated many patients who wished to avoid operation.

He was an outstanding advocate in favour of the rehabilitation of the professional reputation of Morell Mackenzie, and wrote many letters to newspapers and journals on this theme. In 1919 he became the tenant for a decade of Mackenzie's old country house at Wargrave, on the Thames, and in 1921 arranged a memorial service in the churchyard there in connexion with the summer meeting of the Section of Laryngology. He had been given a portrait of Mackenzie by his elder daughter, and when he wished to present this to the Royal Society of Medicine the then president refused to accept it. Irwin Moore, in high dudgeon, did not attend a meeting of the Section of Laryngology again for over 20 years. It is pleasant to relate that a year or two ago the portrait was accepted and hangs in the council room of the Royal Society of Medicine, and Irwin Moore, then in his eighties, became again a welcome attender at the Section of Laryngology.

Irwin Moore had a large and fashionable practice, including royalty from home and abroad. He was distinguished by the courtly manners of the old school, and had a kindly, hospitable, and indeed lovable nature, though his righteous indignation was easily aroused and he could be irascible as well as generous. He had a fishing-lodge down in Radnorshire, and used to dash off there for a week-end's fishing even at an advanced age. He was one of the oldest members of the Savage Club, was happy to be a leading member of the famous old London dining club, the Knights of the Round Table, and for many years was honorary treasurer of the Hunterian Society, in which he took a great interest. His only son died in 1916, his first wife died in 1919, and his second wife and his brother both died last year. Nevertheless he was in active practice and attending patients right up to his last illness, and his ardent spirit was full of vitality to the end.—R. S. S.

W. J. N. VINCENT, C.B.E., M.D.

We record with regret the death of Dr. W. J. N. Vincent at his home at Sheffield on March 15 at the age of 85. He was medical superintendent of the South Yorkshire Asylum from 1911 to 1933. William James Nathaniel Vincent was born on August 24, 1867, the second son of the late Mr. H. J. Vincent, and was educated at the University of Durham and at the London Hospital, graduating M.B., B.S. in 1892 and taking the diplomas of M.R.C.S., L.R.C.P. in the same year. He proceeded to the degree of M.D. in 1914. After acting as assistant medical officer at the Durham County Asylum and at the Borough Asylum, Mapperley Hill, Nottingham, he was appointed assistant medical officer at the South Yorkshire Asylum, Wadsley, Sheffield (now the Middlewood Hospital) in 1898. He succeeded the late Dr. W. S. Kay as medical superintendent in 1911, the same year in which he was appointed to the lectureship in mental diseases in the University of Sheffield. His services in that connexion were officially recognized by the University in 1934, when the honorary degree of M.A. was conferred upon him.

Dr. Vincent, who was accorded the rank of lieutenant-colonel in the R.A.M.C., was in charge of the Wharncliffe War Hospital at Sheffield from 1915 to 1920 and of the Ministry of Pensions Hospital at Wadsley. For his services during the first world war he was appointed C.B.E. in 1919. He took a lively interest in clinical psychiatry and in 1924 was enthusiastic in the use of malarial therapy for general paresis, a method of treatment which might be regarded as a forerunner of more recent physical methods. Among the distinctions which came his way was the presidency of the Sheffield Medico-Chirurgical Society. His keenness on hospital administration and design was exercised during his last years of office by the planning and building of the new admission block at Middlewood, which was opened in 1935. Kind and gentle in manner, and disliking formality, Dr. Vincent was highly esteemed by his colleagues and well loved by his patients. He resigned from the superintendency of his hospital in 1933 and enjoyed many years of retirement. His favourite hobby was painting, and his portrait of Dr. Kay still hangs in the medical superintendent's office at Middlewood Hospital, together with a useful pen drawing of the hospital buildings. Astronomy and alpine climbing were among his other recreations. He married Miss Kate Helen Barker, of Sheffield, in 1917, and she survives him, together with two sons, one of whom is a member of the medical profession, and two daughters.—F. T. T.

J. BARNES BURT, M.D.

Dr. J. Barnes Burt, well known as a rheumatologist on the Continent as well as in this country, died at his home at Bath on March 18 at the age of 72. His death was unexpected, for he had been in active practice until a fortnight before his fatal illness began.

Joseph Barnes Burt was born at Kendal, in Westmorland, in 1880, the son of Dr. J. K. Burt, and was educated at Epsom College and at University College Hospital, qualifying M.R.C.S., L.R.C.P. in 1902, and taking the London M.B. in the same year. He proceeded to the M.D. in 1904. After qualification he held the appointment of house-surgeon at University College Hospital, and then went to Cambridge as a research scholar in special diseases. Deciding to specialize in the treatment of gout, rheumatism, and allied diseases, he set up in practice at Buxton, where he was on the staff of the Devonshire Royal Hospital for many years. During the war of 1914–18 he served as a temporary captain in the R.A.M.C., and was in Mesopotamia from 1917 to 1919. It was relatively late in life, in the year 1935, that Dr. Barnes Burt moved from Buxton to Bath. He was immediately elected to the staff of the Royal Mineral Water Hospital—now the Royal National Hospital for Rheumatic Diseases—and remained an active member from 1935 to 1946, when he retired and was appointed consulting physician. Shortly before the beginning of the last war he was very actively engaged with the plans to rebuild the hospital, and was in fact

chairman and organizer of the medical appeal committee. It was a sad blow to him when the outbreak of war in 1939 put a summary end to the rebuilding, for which the plans had been proposed and most of the money collected.

Barnes Burt was the first president of the Section of Physical Medicine of the Royal Society of Medicine and a past chairman of the International Society of Medical Hydrology. On the death in 1940 of Dr. Fortescue Fox, who was the creator and father of the society, Barnes Burt took over the chairmanship, and largely through his efforts the society was revived at the end of the last war. When the British Medical Association held its Annual Meeting at Plymouth in 1938 he served as a vice-president of the Section of Physical Medicine and Physical Education. He had interested himself in the work of the Association some years before the Plymouth meeting, however, and was a member of the Spa Practitioners Group Committee from 1927 to 1946. He also served on the Physical Medicine Group Committee from 1945 to 1950, and was chairman of the Bath Division in 1932–3. A fine physician and a cultivated and a forthright colleague, he will be deeply missed. His kindness and consideration inspired a real affection in both his patients and his colleagues. During his long association with the treatment of the rheumatic diseases he wrote extensively, particularly on gout and neuritis.

Among his other activities Barnes Burt was a city councillor in Bath from 1939 to 1946, representing the Bathwick ward. He was an authority on etchings and water colours, and among his collection were some fine examples by Rembrandt and John Cotman. His own efforts in this field were of a high standard. At one time he was a governor of the Whitworth Art Gallery.

He married Miss Dorothy Armitage, and she survives him, together with the two sons and one daughter of the marriage. His eldest son has followed his father not only into the medical profession but also as president of the Section of Physical Medicine of the Royal Society of Medicine.—L. C. H.

Medico-Legal

MEDICAL EVIDENCE ON INSANITY

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The vexed question of the respective functions of the jury and of medical expert witnesses was once again ventilated in the Court of Criminal Appeal on March 30.[1]

The appellant, Joseph Holmes, had been convicted at Nottingham Assizes of the savage and frenzied murder of his landlady and duly sentenced to death. His defence was that of insanity, and it was conceded by the prosecution that he suffered from paranoic schizophrenia. After the murder he had gone to the police station, had told the police that he had killed his landlady, and had made a full statement about it. Under the M'Naghten rules the issue for the jury on which criminal responsibility for his act depended was the state of his mind at the time the act was done—that is, did he know what he was doing, and, if so, did he know that what he was doing was wrong?

The principal ground of the appeal was that one of the medical witnesses called on this issue had been asked whether in his opinion the appellant's conduct in going to the police immediately after the murder and making a full statement would indicate that the appellant had known that what he was doing was wrong in law. This, argued counsel, was an improper question, in that a medical man, however eminent, should not be asked his opinion on the very question which it was for the jury, not for the expert witness, to decide. He submitted that a doctor, having first proved that the accused was suffering from a disease of the mind, might then be asked whether in his experience such a disease would affect his judgment of right and wrong, but that he must not be asked what was in the man's mind when the act was done.

During the argument the Lord Chief Justice, Lord Goddard, interjected to ask what was the point of the appeal, since everyone was now agreed that the appellant was certifiably insane. Whatever the result of the appeal the appellant would become a patient in Broadmoor. Counsel replied that, though the matter in respect of this appellant might be academic, it was one of general importance, and, if the judge at the trial had been wrong in allowing the question to be put to the doctor and answered, this ought to be plainly laid down by the court.

The judgment of the court dismissing the appeal was given by the Lord Chief Justice. He said that the doctor called for the defence was asked in cross-examination whether in his view the appellant's behaviour when he went to the police indicated that he knew that what he was doing was wrong in law. No member of the court had ever heard of objection being taken to such a question. If the answer the doctor had given to the question had been "No," to exclude the question might have placed an insuperable difficulty in the way of the defence. The court considered the question to be a perfectly proper one, and one which if held inadmissible could possibly produce injustice in the case of an innocent prisoner.

The court might well have gone further and asked how in the world a jury of twelve laymen could draw a conclusion about what was in the mind of a paranoic schizophrenic without the assistance of the opinion of a doctor with professional experience of that condition being given upon that very question. On the opinion being given, it is of course the responsibility of the jury to make up their minds whether it is an opinion on which they ought in conscience to act.

[1] *The Times*, March 31.

Medical Notes in Parliament

INQUIRY INTO HEALTH SERVICE COSTS

The MINISTER OF HEALTH announced on April 1 his decision, taken in conjunction with the Secretary of State for Scotland, to refer the costs of the National Health Service to an independent committee for investigation. The chairman of this committee will be Mr. C. W. Guillebaud, a Cambridge don and economist, who has served on a number of trade wages councils and industrial arbitrations. The names of the other members are to be made known as soon as possible.

Mr. Iain Macleod, in his statement, said that he and the Secretary of State for Scotland had had under close review the whole problem of the present and future cost of maintaining a proper and adequate National Health Service. They had already initiated a number of administrative and other measures designed to alleviate, so far as possible, the considerable cost to the taxpayer without impairing the quality of the service provided. But these were inevitably measures of detail and the general long-term problem remained essentially unsolved. After a great deal of thought the Secretary of State and he both felt that the many issues involved in this problem were so complex that the wisest course would be to refer the whole matter for an independent and objective inquiry by a committee. They therefore proposed to appoint a small committee with the following terms of reference:

To review the present and prospective cost of the National Health Service; to suggest means, whether by modification in organization or otherwise, of ensuring the most effective control and efficient use of such Exchequer funds as may be made available; to advise how, in view of the burdens on the Exchequer, a

rising charge upon it can be avoided, while providing for the maintenance of an adequate Service; and to make recommendations.

Opposition Protests

The announcement provoked an immediate storm of protest among Opposition Members. Mr. ANEURIN BEVAN assailed it as an abuse of Parliamentary procedure, because immediately after the Easter recess there was to be the Budget, which naturally bore on the cost of the Health Service. That was the appropriate time for this kind of statement. Had the Cabinet seriously decided that this was an issue to be remitted to a committee of inquiry? It was primarily a matter for the House of Commons and for political decisions. This was an act of the most unprecedented political cowardice—to send to a committee of inquiry a matter which was at the centre of British politics. Why had the Minister not asked the Central Health Services Advisory Council for its advice about modifications in the organization of the Service? It had been set up for that purpose. What the Minister was doing as a consequence of struggles between himself and the Treasury was seeking another instrument by which he might mutilate the Service. Everyone knew the Minister was an avowed enemy of the National Health Service. He had publicly declared it, and in his own hands it had received many grievous blows. The best service he could render to it would be to resign.

Long-term Problem

Mr. MACLEOD said that he had seen Mr. Guillebaud the previous afternoon, and thought it was his duty to inform the House as soon as he could. The matter had been considered at the highest level by the Government, who thought that it was essentially a departmental matter and that the announcement should be made by him and not by the Chancellor of the Exchequer as part of the Budget, because it was the long-term problem which remained essentially unsolved. It was because the Central Health Services Advisory Council was representative of wide interests within the Service that he did not consider it to be the appropriate body for an inquiry of this nature. In his view what was needed was an entirely independent inquiry—not a political one, nor one linked in any way to membership of a committee or tied to any of the professions in the Health Service. He would never have agreed to the committee, nor would Mr. Guillebaud have accepted the chairmanship, if it had been designed to mutilate the Health Service. On a matter that so deeply concerned the finances of the Service the House would give the fullest value to the view of a Minister of Health who never got his estimates to within £100m. of the right figure.

Mr. BEVAN retorted to the last observation that on his last estimate expenditure was £14m. less. Was expenditure equal to £400m. of the National budget, and concerning the welfare of all the citizens of Great Britain, a fit subject to be remitted to a committee of inquiry? Why did not the Chancellor of the Exchequer remit to such a committee the question whether taxes should be higher or not? Why did he not hand over the whole of his Budget to such a committee? What the Minister was doing was to seek the most respectable auspices under which to destroy the Health Service.

In the considerable uproar Mr. C. J. M. ALPORT protested that a vicious personal attack was being made on the Minister; and Mr. S. SILVERMAN said the Minister had taken a large chunk of public expenditure and proposed a revolutionary and unconstitutional method of dealing with it. Mr. BEVAN repeated that an essential feature of the Budget would be expenditure on the Health Service, and the purpose of this statement by Mr. MACLEOD, made so shortly in advance of the Budget, was to nullify a great deal of the discussions on the Budget.

Mr. R. FORT, on the other side, said that many, inside and outside the House, would welcome the Minister's statement. It would enable a great deal of information about the cost and expenditure on the Service to be brought together in a form which could be appreciated. In putting the matter before the committee, he asked, would the Minister ask its opinion about the effect of making block grants to hospitals to give regional boards greater independence than they had enjoyed under the organization set up by Mr. Bevan? Mr. MACLEOD said that it was true that many people had for a long time considered that this was a matter which should be inquired into. The question of block grants came within the terms of reference.

Mr. A. WOODBURN suggested that as an economist was being put in charge of the inquiry the purpose of the committee was to find out, as the Organization and Methods Division of the Treasury could, whether the existing Service could be more economically run. Mr. MACLEOD said that this was a general inquiry into the financing of the Service. It was not an economy cuts committee. He thought a committee not tied to the professions nor to any political party was the best way of dealing with a long-term matter, which might take months and perhaps a year.

Free Drugs for Private Patients

Sir EDWARD KEELING asked the Minister of Health on April 2 how much it would cost the taxpayer to give drugs, dressings, and appliances to private doctors' patients after deducting the 1s. prescription charge, but without allowing for the transfer of many National Health Service patients to private doctors which would follow such gift. Miss PAT HORNSBY-SMITH informed him that if the net cost per person were the same as for patients under the National Health Service (which assumed that private doctors would be bound to observe the same conditions as National Health Service doctors) the total cost to the taxpayer might be nearly £1½m. per annum.

Untreated Flour

Viscount HINCHINGBROOKE asked the Minister of Food on April 1 whether he was aware of fresh evidence that consumption of wheat-flour treated with nitrogen trichloride (agene) or chlorine dioxide produced eczema and mental disturbance in allergically responsive persons and what steps he was taking to make chemically untreated flour or bread available to such persons and to those who preferred it. Major G. LLOYD GEORGE said he assumed that Lord Hinchingbrooke was referring to a recently published article in a medical journal (*Lancet*, 1953, **1**, 577) reporting a single case of allergic response to flour treated with agene or chlorine dioxide. He was assured that flour which had not been treated with either of these improvers, and bread made from such flour, would, as hitherto, be available on special request.

Industrial Noise

Dr. BARNET STROSS questioned the Minister of Labour on March 31 about the effect of noise in metal-working industries on hearing, and the steps being taken to protect the workers from deafness of this type.

Mr. HAROLD WATKINSON, the Parliamentary Secretary, replied that the department was aware of the recent report of a committee of the Medical Research Council on the medical and surgical problems of deafness and that exposure over many years to noise above certain intensities might cause deterioration in hearing. Much research was being carried out into this question, and a committee had been set up jointly by the Department of Scientific and Industrial Research and the Medical Research Council which would consider, among other things, the effect of noise in relation to human efficiency. The harmful effects of noise on the individual could be reduced to some extent by the wearing of protective ear coverings and by eliminating injurious noise at its source by improved designs of machines and their mountings and the sound insulation of walls and ceilings; but the subject had been found to bristle with practical difficulties. He added that there was to be specific research into finding the right type of protective ear covering.

Hospital Staff Wage Awards.—The estimated cost in 1953–4 of wage and salary awards made to all full- and part-time hospital staff during the last 12 months was approximately £6¼m.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending March 21 (No. 11) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	20	3	10	0	1	53	5	9	0	1
Dysentery	433	41	102	9	1	642	57	35	1	1
Encephalitis, acute	6	1	0	0		3	0	4	0	
Enteric fever:										
Typhoid	3	0	1		1	4	1	0	0	1
Paratyphoid	2	0	0			7	0	3 (B)	1	1
Food-poisoning	47	11		0		117	13		0	
Infective enteritis or diarrhoea under 2 years				12	15				12	18
Measles*	27,226	1439	434	202	200	7,121	256	514	303	279
Meningococcal infection	49	6	15	1	3	46	7	12	1	6
Ophthalmia neonatorum	39	2	4	0		33	4	10	1	
Pneumonia†	1,044	61	347	10	4	950	38	506	13	3
Poliomyelitis, acute:										
Paralytic	20	0	2	1		13	0	0	2	1
Non-paralytic	6	1				9	1			
Puerperal fever‡	256	40	8	2		240	35	4	1	2
Scarlet fever	1,625	94	178	41	47	1,546	118	211	24	72
Tuberculosis:										
Respiratory			188	28				146	42	
Non-respiratory			39	3				33	4	
Whooping-cough	3,104	202	320	23	88	3,086	158	310	163	91

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	1	0	0	0	0	1	0	0
Dysentery	0	0	0	0		0	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0	0				0	0		0	
Infective enteritis or diarrhoea under 2 years	13	0	2	1	1	8		0	1	1
Influenza	133	16	14	0	4	33	3	23	0	1
Measles		1	0	0	1		0		0	0
Meningococcal infection		0	0				0	1		
Pneumonia	365	56	25	26	17	322	53		12	6
Poliomyelitis, acute	0				0	1	0			0
Scarlet fever		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory	120	14	15	6	9	142	26	27	4	13
Non-respiratory		0	2	0	1		2	3	2	1
Whooping-cough	1	0	0	0	0	7	0		0	1
Deaths 0–1 year	253	28	20	12	14	259	34	29	9	16
Deaths (excluding stillbirths)	6,207	879	644	148	204	5,732	875	712	128	170
LIVE BIRTHS	8,182	1215	913	216	318	8,072	1203	957	228	437
STILLBIRTHS	220	27	18			198	32	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Vital Statistics

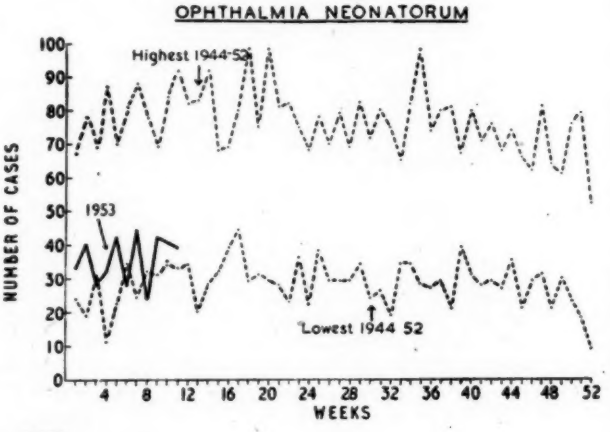
Smallpox in the North Country

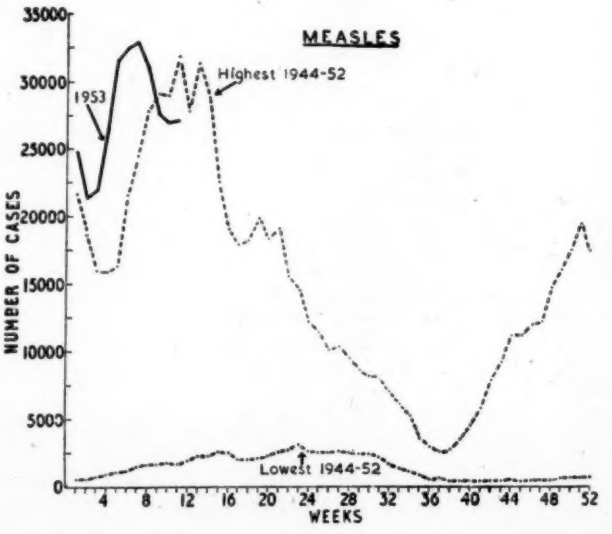
Up to noon, April 7, 21 cases of smallpox, including 4 deaths, had been reported from Yorkshire and Lancashire. Cases (deaths in parentheses) were distributed as follows:—*Todmorden M.B.:* 11 (3); *Bacup M.B.:* 2 (1); *Oldham C.B.:* 2; *Bury C.B.:* 2; *Halifax C.B.:* 4. Five cases have been notified since last week's report (which made the erroneous statement that 2 cases in Todmorden M.B. were both contacts of a new Bacup case). The new cases were as follows:—*Halifax C.B.:* 4 cases, which were contacts of one of the original cases at Halifax General Hospital; *Oldham C.B.:* 1 case, which was a contact of a previous case. Cases continue to be in the direct lines of contact with previous cases, and the outbreak appears to be well contained.

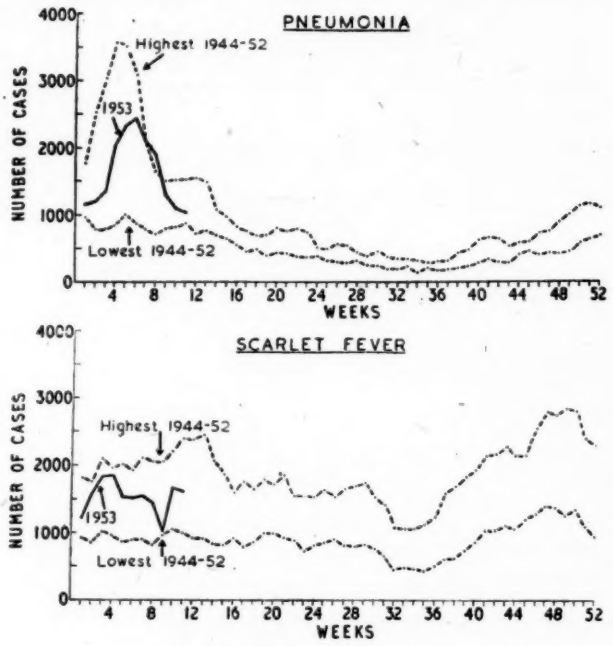
In reply to a question in Parliament, the Minister of Health stated on April 2 that of the 19 cases confirmed up to the previous day 10 had had no original vaccination, 7 had not been vaccinated since infancy, and 2 had been vaccinated in infancy and again in the 1914–18 war. After the outbreak had started 14 were vaccinated or revaccinated.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus --------, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

The largest fluctuations in the returns of infectious diseases during the week ending March 21 in England and Wales were a rise of 302 in the number of notifications of measles, from 26,924 to 27,226, 71 for dysentery, from 362 to 433, and a fall of 50 for scarlet fever, from 1,675 to 1,625.

The largest rises in the number of notifications of measles were 251 in Hertfordshire, from 858 to 1,109; 127 in Worcestershire, from 346 to 473; and 106 in Cornwall, from 263 to 369; and the largest falls were 250 in Essex, from 1,615 to 1,365; 156 in Surrey, from 1,961 to 1,805; 107 in Kent, from 1,415 to 1,308; and 103 in Oxfordshire, from 434 to 331. Only small fluctuations occurred in the local trends of scarlet fever. The notifications of whooping-cough rose from 3,072 to 3,104; the largest fluctuation was an increase of 67 in Lancashire, from 528 to 595. 20 cases of diphtheria were notified, 11 fewer than in the preceding week. A decrease in Lancashire from 10 to 5 was the chief feature of the returns of diphtheria.

26 cases of acute poliomyelitis were notified; these were 5 more for paralytic and 4 more for non-paralytic cases than the preceding week. The largest return was 3 in Sussex.

The largest centres of dysentery were Lancashire 80 (Liverpool C.B. 40), Leicestershire 64 (Leicester C.B. 63), London 41, Middlesex 43 (Edmonton M.B. 31), Yorkshire West Riding 37 (Leeds C.B. 12), and Cheshire 17.

133 deaths were attributed to influenza in the great towns, 6 fewer than in the preceding week.

Industrial Accidents and Disease

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in February was 121, compared with 101 in the previous month and 114 (revised figures) in February, 1952. The number of cases of industrial disease reported was 41, including 3 from lead poisoning, 4 from anthrax, 14 from epitheliomatous ulceration, and 20 from chrome ulceration. There were no deaths.—*Ministry of Labour Gazette*, March, 1953.

The Services

A *Supplement* to the *London Gazette* has announced the following awards:

First Clasp to the Territorial Efficiency Decoration.—Major A. M. Rennie, R.A.M.C.

Territorial Efficiency Decoration.—Major A. M. Rennie, Captain (Honorary Major) D. R. Beaton, and Captain H. J. Minford, M.C., R.A.M.C.

Medical News

Association of the Royal College of Surgeons in Ireland.—The annual general meeting of the association was held in the Royal College of Surgeons in Ireland on March 21 with the president, Dr. Paul Murray, in the chair. Professor A. K. Henry, professor of anatomy at the R.C.S.I. and emeritus professor of clinical surgery of Cairo University, was elected president for 1953–4. Dr. J. D. H. Widdess was elected vice-president, Dr. Catherine A. Quinn hon. treasurer, Dr. P. D. J. Holland hon. record secretary, and Mr. W. A. L. MacGowan hon. corresponding secretary.

Medical Aspects of Civil Aviation.—The standing medical committee of the International Air Transport Association held its third annual meeting at Estoril, Portugal, during the week March 21 to 28. The members represented 18 international airlines, and Sir Harold Whittingham was in the chair. The committee discussed the practical application of the W.H.O. International Sanitary Regulations, medical requirements for aircrew, medications contra-indicated for use by aircrew when on duty, methods of disinfection of aircraft, and the maintenance of wholesome water supplies on aircraft. It was considered that aircraft could be kept virtually free of insects if fabric and paint were impregnated with a synthetic resin containing an effective insecticide. This would save time in transit and the personal annoyance caused by aerosol spraying.

Bravery in Kenya.—The award of the M.B.E. (Civil Division) to Mrs. Dorothy Meiklejohn, M.R.C.S., L.R.C.P., of Aberdare District, Kenya, was gazetted in London on March 27. The citation was as follows:

On an isolated farm Mrs. Meiklejohn and her husband were in their sitting-room when, suddenly, four Africans burst into the room and immediately launched a savage attack on them. At least one of the Africans was armed with a pistol, while the others were in possession of native knives. Mrs. Meiklejohn shouted to her husband and tried to reach for a firearm which was in her handbag, but was slashed on the wrist. Both Mrs. Meiklejohn and her husband were attacked again and again until the Africans thought they were dead; they then left. Mrs. Meiklejohn's husband climbed the stairs to his bedroom and collapsed there. Mrs. Meiklejohn was suffering from multiple and very serious wounds. Her face and arms were slashed and she was fast losing blood, but, determined to obtain help for her injured husband and raise the alarm, she staggered to her car and drove to the police station, at Thomson's Falls, a distance of nine miles, over a rough and lonely road. On arrival she was only able to identify herself before she collapsed. She was taken to hospital and recovered, but her husband succumbed to his injuries.

Mrs. Meiklejohn showed outstanding fortitude in the face of grave danger.

Award of Manson and Chalmers Memorial Medals.—The council of the Royal Society of Tropical Medicine and Hygiene has awarded the Manson Medal, 1953, to Professor Jérôme Rodhain, director of the Institute of Tropical Medicine, Antwerp. The medal is awarded triennially to the living author of original work in any branch of tropical medicine or hygiene. The Chalmers Memorial Medal, 1953, has been awarded by the council to Mr. D. J. Lewis, medical entomologist in the Sudan Government Service. This medal is awarded biennially for research of outstanding merit on tropical medicine or hygiene. Only those under 45 years of age are eligible.

Dangerous Drugs.—Two new Statutory Instruments affecting dangerous drugs came into force on March 31. The first, the Dangerous Drugs Regulations, 1953, consolidates and amends certain earlier Regulations and, apart from a few scheduled exceptions, applies to all substances covered by the Dangerous Drugs Act, 1951. The second, the Dangerous Drugs Act (Relaxation) Order, 1953, frees morpholinylethylmorphine from control by Subsection (1) of Section 11 of the Dangerous Drugs Act, 1951. This drug, which is obtained from one of the phenanthrene alkaloids of opium, is now controlled by Part III of the new Regulations.

Sir Howard Florey, F.R.S., is on a three months' visit to Canberra in his capacity as adviser to the Australian National University on the John Curtin Memorial School of Medical Research.

Dr. William Storrar, formerly assistant administrative medical officer of the South-western Regional Hospital Board, has been appointed medical director of the Montreal General Hospital. He graduated from Edinburgh in 1939, and went to Canada in 1951.

Professor R. M. Titmuss, formerly a member of the Medical Research Council's Social Medicine Research Unit and now professor of social administration at the London School of Economics, has been appointed a member of the National Insurance Advisory Committee.

The Rev. A. C. Irvine, M.D., senior missionary of the Church of Scotland Mission in Kenya, is to receive the honorary degree of D.D. at the summer graduation at Aberdeen University.

COMING EVENTS

National Association for the Prevention of Tuberculosis.—A meeting for members of all sections of the N.A.P.T. is to be held in the Great Hall, B.M.A. House, Tavistock Square, London, W.C.1, on Saturday, April 18, at 2.30 p.m. The subject to be discussed is "The Modern Management of Tuberculosis by Chemotherapy and Otherwise." Application for tickets should be made as early as possible to the National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1.

Seminar on World Health.—During the World Health Assembly at Geneva the World Federation of United Nations Associations is organizing a Seminar to be held at the Palais des Nations in Geneva from May 4 to 15. The Seminar will be opened by Dr. Brock Chisholm, and there will be lectures on world health problems. Applications may be sent through a United Nations Association or directly to the World Federation of United Nations Associations, 1, Avenue de la Paix, Geneva, or 19, Avenue Kléber, Paris, 16.

NEW ISSUES

British Journal of Industrial Medicine.—The next issue (Vol. 10, No. 2) will be available in a week's time. The contents include:

RESPIRATORS FOR PROTECTION AGAINST MERCURY VAPOUR. V. B. Vouk, Z. Topolnik, and M. Fugas.
THE ACTION OF FLINT OF VARIABLE SIZE INJECTED AT CONSTANT WEIGHT AND CONSTANT SURFACE INTO THE LUNGS OF RATS. E. J. King, G. P. Mohanty, and C. V. Harrison.
DUST SAMPLING TO SIMULATE THE HUMAN LUNG. H. H. Watson.
PNEUMOCONIOSIS OF COAL-MINERS IN SCOTLAND. John Black.
A PILOT INVESTIGATION INTO THE OCCURRENCE OF PNEUMOCONIOSIS IN LARGE POWER STATIONS IN SOUTH WALES. Idris Davies.
EXPECTED FREQUENCY OF BLADDER TUMOUR IN WORKS POPULATION. R. A. M. Case.
METHYLOCTYLBENZENE SULPHATE: A NEW INDUSTRIAL SENSITIZING AGENT. C. N. D. Cruickshank and H. Howard-Swaffield.
PSYCHOLOGICAL HANDICAP IN RELATION TO PRODUCTIVITY AND OCCUPATIONAL ADJUSTMENT. M. Markowe and L. E. D. Barber.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.

Abstracts of World Medicine.—The April issue (Vol. 13, No. 4), which is now available, contains abstracts of important papers on both medical and surgical subjects drawn from the medical literature of some 20 different countries and of all five continents. In addition to clinical medicine and surgery, the subjects covered include pathology, bacteriology, pharmacology, and chemotherapy, and there are also sections dealing with public health, industrial medicine, forensic medicine and toxicology, aviation medicine, anaesthetics, radiology, and the history of medicine.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; a specimen will be sent free on request.

These journals are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 13

MEDICAL SOCIETY OF LONDON.—8.30 p.m., meeting of Fellows. Discussion to be introduced by Dr. K. Harris and Dr. S. Oram: Early Manifestations of Coronary Disease.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. F. Masina: Surgical Approach to Tumours of the Bladder; 6.30 p.m., Mr. V. H. Riddell: Thyroid Tumours.
ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Astigmatism and its Treatment. Factors Affecting Binocular Vision.

Tuesday, April 14

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Dr. E. A. Carmichael: Hemiplegia of Early Onset and the Results of Hemispherectomy.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. R. Furlong: Pseudocoxalgia; 6.30 p.m., Mr. P. Clarkson: Injuries of the Hand.

Wednesday, April 15

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, W.C., 4.30 for 5 p.m., Dr. E. G. B. Calvert: Surgery and the Diabetic.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Professor Lambert Rogers: Costoclavicular Syndrome; 6.30 p.m., Mr. Harold Edwards: Treatment of Inguinal Hernia.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. B. E. Schlesinger: Tuberculosis in Childhood (Illustrated).

Thursday, April 16

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Dr. A. E. Jones: Clinical Aspects of Carcinogenesis; Dr. A. Glucksmann: Histological Aspects of Carcinogenesis.
EPSOM AND SUTTON INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At Horton Hospital, Epsom, 5.30 p.m. Films: (1) Dr. T. F. Main: Grief; (2) Dr. H. R. Rollin: three short films illustrating manic and depressive psychoses.
FARNBOROUGH HOSPITAL, Kent.—5.30 p.m., Dr. C. J. Gavey: Physician's Evaluation of Surgical Risks.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At 11, Chandos Street, W., 8.30 p.m., Dr. Michael Kremer: Modern Views on Epilepsy and its Treatment.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Dr. E. A. Carmichael: Hemiplegia of Early Onset and the Results of Hemispherectomy.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Dr. Kenneth Perry: Tuberculous Glands of Neck; 6.30 p.m., Mr. Cecil Flemming: Fractures of the Foot.
ROYAL EYE HOSPITAL.—5.30 p.m., Miss J. M. Dollar: Problem of Iridocyclitis and its Investigation.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor W. C. W. Nixon: Physiological and Clinical Aspects of Uterine Action.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. A. S. Paterson: postgraduate demonstration in neurology.
SOCIETY OF CHEMICAL INDUSTRY: MICROBIOLOGY GROUP.—At Medical Society of London, 6.15 p.m., Dr. Lois Dickinson: Use of the Bacteriophage in the Study of Viruses; Mr. L. J. Meanwell: Bacteriophages of the Lactic Streptococci.

Friday, April 17

BRITISH INSTITUTE OF RADIOLOGY.—5 p.m., meeting of medical members; 6.30 p.m., Professor J. Rotblat: Study of the Distribution of Thorotrast in the Body by Autoradiography.
FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4 p.m., Professor R. J. V. Pulvertaft: Study of Radiosensitivity in Vitro; Dr. Edith Paterson: Factors Influencing Recovery after Whole Body Radiation; Dr. W. M. Court Brown: Some Aspects of Water and Electrolyte Metabolism in Radiation Sickness.
KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.
LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8.30 p.m., Mr. C. E. Shattock: Lumps in the Breast.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.30 p.m., Mr. Roland Jones: Surgery of Peripheral Vascular Disease.
ROYAL EYE HOSPITAL.—4.30 p.m., Mr. A. J. Cameron: Problem of Retinitis Pigmentosa.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Brittain.—On March 21, 1953, at the Christopher Nursing Home, Wigan, Lancs, to Dr. Ina (formerly Eakins), wife of Dr. George Brittain, a daughter.
Eason.—On April 2, 1953, at the Lambeth Hospital, London, S.E., to Ruth (formerly Towler), wife of Thomas John Eason, F.R.C.S.Ed., a brother for Robert and Charles.
Griffiths.—On March 26, 1953, at Overton Lea Maternity Home, Cheltenham, Glos, to Elizabeth, wife of Dr. Eric Griffiths, a daughter—Lynn Elizabeth.
Johnston.—On March 26, 1953, at the Varborough Nursing Home, Southsea, Hants, to Kay, wife of Dr. C. L. Johnston, a brother for Heather and Moya.
Levien.—On March 26, 1953, at Hamilton, New Zealand, to Norah Margaret (formerly Mathers), wife of G. H. Levien, F.R.C.S., a daughter.

MARRIAGES

Owen—Griffith.—On March 28, 1953, at Moriah Chapel, Caernarvon, Kelyth Lloyd Owen, M.R.C.S., L.R.C.P., to Jean Griffith.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Sound-proofing the Surgery

Q.—*What are the best ways of sound-proofing a doctor's surgery? Often attempts seem to fail because of leakage at the door.*

A.—As a general rule the insulation of the partitions themselves will be adequate if they are of brick or breeze, and plastered. Even a timber stud partition has moderate insulation if constructed with heavy lath and plaster, and it is only likely to give trouble when it is a light or temporary structure such as fibreboard or plain plasterboard on a light framing. Weight is the main requirement. For new work, therefore, I would suggest 4½ in. (11.5 cm.) brick if possible, but 3 in. (7.6 cm.) clinker concrete plastered ½ in. (1.3 cm.) thick on both sides would be reasonable.

Any weakness in a sound-insulating barrier has a marked influence on the overall insulation. In the case of surgery partitions the weakest part of the insulation is almost invariably the doorway, the leakage of sound being due to a double cause : (*a*) the air gaps round edges of the door, especially at the bottom ; and (*b*) the door itself (or the door panels) being lighter than the main partition structure—the lighter the weight the poorer the insulation.

In taking remedial action the first step is to aim at sealing the air gaps all round the door. This can be done fairly well by means of metal draught-strip, in conjunction with a splayed or rebated threshold. An alternative method is to put rubber strip all round the door stop, but the door must be made to close tightly against it. The door itself must be reasonably heavy—either solid wood throughout or with thick panels, or covered with a heavy sheet material. Nevertheless, however heavy the door or however well sealed the edge gaps, the doorway will nearly always remain the weak point in the partition unless double doors are provided, separated either by an air space of not less than 6 to 8 in. (15 to 20 cm.), or better still by a lobby. The airspace or lobby should contain as much absorbent-lined surface as possible—say "acousti-celotex" or similar tiles fixed to the reveals, to the wall and ceiling, or to the door face. Double doors are certainly recommended whenever possible, both for new work and for adaptations. Single doors, even if heavy and with very tight closure all round, do not give real privacy.

If the surgery is sparsely furnished it may also be useful (in addition to the measures for sound insulation) to provide a reasonable area of absorbent treatment (acoustic tiling) on the ceiling and/or wall surfaces ; but this is not worth while if the room already has a carpet and curtains and some upholstered furniture.

Best Antibiotic in Meningitis

Q.—*What is the best antibiotic to use initially in meningitis due to the following organisms : (a) Haemophilus influenzae, (b) Pseudomonas pyocyanea, (c) Bact. coli, (d) Proteus vulgaris, and (e) Strep. faecalis? Please indicate dosage and route of administration.*

A.—(*a*) *H. influenzae* is at least moderately sensitive to all the main antibiotics as well as to sulphonamides, and succeeding years have witnessed the use of sulphadiazine, penicillin, and streptomycin individually and in combination, and with or without antiserum. Still better results have more recently been obtained with both aureomycin and chloramphenicol. The organism is highly sensitive to both : chloramphenicol is probably to be preferred because it attains higher concentrations in the cerebrospinal fluid (one-third to one-half of those in the blood, a level unapproached by any other antibiotic). The dose should be 200 mg. per kg. body weight per day in divided doses by the mouth.

(*b*) *Ps. pyocyanea.*—The antibiotic to which this species is most sensitive, and regularly so, is polymyxin. It must be injected intrathecally in daily doses of 20 mg. If systemic as well as meningeal infection exists, it may also be given intramuscularly (an average dose is 2.5 mg. per kg. body weight daily), but prolonged systemic treatment involves a risk of renal damage. The second choice is streptomycin, *provided that the strain is sensitive* (this must be tested: some are totally resistant). This also must be given intrathecally, the initial dose being 100 mg. daily. The newer antibiotics are less useful and penicillin useless. Failing anything else, full doses of sulphadiazine may help.

(*c*) *Bact. coli* meningitis is probably best treated with streptomycin if the strain is sensitive : chloramphenicol would be the second choice.

(*d*) *Proteus vulgaris.*—This form of meningitis is fortunately so rare that there are no adequate data on which to base any dogmatic statement about treatment. The organism is relatively insensitive to the three newer antibiotics, and streptomycin again offers the best hope of success, but with the same proviso as before.

(*e*) *Strep. faecalis.*—The rarity of this infection again precludes confident judgment, but the antibiotic to which this species is most sensitive by far is aureomycin : the dosage (exclusively oral) should be as for chloramphenicol (see *(a)*). In view of the synergic action of penicillin and streptomycin in endocarditis due to *Strep. faecalis*, it is possible that this combination might also be effective in meningitis due to it.

All the suggestions made are based on normal bacterial sensitivities, and should serve for initial treatment, but this may have to be varied in some cases following laboratory studies. There is no condition in which accurate assessment of the susceptibility of the organism to all appropriate and available chemotherapeutic agents is more important or more urgent than meningitis due to such awkward bacteria as those named here. The doses stated are those for adults : about one-quarter of these is usually given to infants.

Infectious Diseases and Public Laundries

Q.—*I have recently seen a leaflet which states : "Since May, 1952, tuberculosis has been a notifiable infectious disease, and the 1936 Public Health Act requires that all materials contaminated by the organisms of notifiable infectious diseases must be sterilized before being sent to a public laundry." Is it therefore illegal for a tuberculous person in an infectious state to send his washing to a public laundry?*

A.—The statement is incorrect. It was probably inspired by a misinterpretation of the Public Health (Tuberculosis) Regulations, 1952 (Statutory Instrument No. 904 of 1952), which came into force on May 1, 1952.

The nomenclature in respect of the notification of infectious disease tends to be confusing and may be briefly summarized thus :

S.144 of the Public Health Act, 1936, requires the notification of a "notifiable disease" to the local medical officer of health. "Notifiable disease" is defined in s.343, and the provisions of the Act apply *only* to the diseases thus defined. A local authority may add to the list of notifiable diseases so far as its own area is concerned in accordance with the provisions of s.147. It will be seen, therefore, that there are two types of "notifiable disease," (*a*) those specifically mentioned in s.343, which applies to all local authorities in England and Wales, and (*b*) those added by the local authority with the Minister's approval and having a territorial limitation. Both types are "notifiable diseases" and the sections of the Public Health Act (s.144–153, s.155–160) dealing with the notification and prevention of "notifiable diseases" apply to them.

By s.143 of the Public Health Act, 1936, the Minister of Health may make Regulations regarding the treatment and prevention of spread of infectious, epidemic, or endemic disease. The Minister

has exercised this power so as to require the notification of a number of diseases not notifiable under the Public Health Act, 1936—e.g., plague, malaria, measles, tuberculosis, etc. Diseases thus declared notifiable by the Minister are not "notifiable diseases" within the meaning of that term defined in the Public Health Act, 1936, and the provisions of that Act do not apply to them.

The Public Health (Tuberculosis) Regulations of 1952 merely revoke and re-enact the Public Health (Tuberculosis) Regulations, 1930, with minor administrative changes rendered necessary by the National Health Service Acts.

I do not know of any statutory prohibition on a tuberculous person in an infectious state sending his washing to a public laundry, but he might well incur a common law liability if damage resulted from his action. It is general practice in the laundry trade for the terms of the contract between laundry and customer to contain a clause excluding "infected articles" until they have been disinfected. In any event there is a moral duty not to spread infection, and the public should be thus advised.

"Cortisone Fractures"

Q.—*What is the mechanism of fracture of the spine during cortisone therapy?*

A.—Fracture-collapse of the vertebrae during cortisone therapy is due to osteoporosis and increased functional activity. Osteoporosis is in most cases the result of prolonged inactivity, usually bed-rest in cases of rheumatoid arthritis; occasionally it is of the senile type. If cortisone has been given for prolonged periods, it may have some slight additional effect, since it tends to produce osteoporosis. (This is well seen in Cushing's syndrome, essentially a hypercorticoid state.) However, collapse is sometimes seen in rheumatoid patients being enthusiastically "rehabilitated" without any cortisone treatment. The increased mobility following the loss of pain and stiffness on cortisone is probably the major factor in the production of these "cortisone fractures."

Premature Orgasm in the Female

Q.—*A woman of 38 years and married 15 years says that her marriage has been marred by the fact that she experiences a sudden premature orgasm after which she cannot bear her husband to touch her. What are the possible causes of this condition? She states that she is very anxious to have a child and the only time that she remembers being at all happy in her married life was once when, her period being late, she thought that she might be pregnant. What treatment is advised?*

A.—Once a woman has reached orgasm it is usual for coitus to become difficult because the secretions dry up and the pelvic muscles contract to close the vagina. However, such strong aversion to continued attempts by the husband is abnormal. Premature orgasm in the female is also exceptional. Indeed, the account of the case suggests that the main symptom is only a cloak to a more important background, and sympathetic probing of the problem by the family doctor or by a psychologist might well help to elucidate the picture. The most obvious possible basis for the trouble is the sterility, and the best approach might well be to investigate both husband and wife from this standpoint. If sterility is the real problem, and if investigation shows that there is no absolute bar to conception in either partner, artificial insemination using the huband's semen might well circumvent the immediate problem of coitus and result in pregnancy. If the wife achieved a pregnancy by this or other means, her emotional upset might settle and this lead to spontaneous cure of her other symptoms.

Other questions which arise are: How long does the husband take to achieve orgasm? Does he in fact have an emission, or is he suffering from partial impotence?

If it be decided to treat the case symptomatically, orgasm in the wife might be deferred if preliminary love play is omitted entirely and by coitus *a tergo*.

NOTES AND COMMENTS

Alcohol and Barbiturates.—Dr. D. R. WOOD (Sheffield) writes: I was interested in the reply under "Any Questions?" (January 24, p. 232) to a query about alcohol and barbiturates. I wonder in what sense your expert is using the words "potentiated" and "synergistic"? In the papers to which the reader is referred the question is dealt with from the point of view of the LD50 of each substance. From the point of view of "drunk in charge" it would be important and interesting to know whether the substances reinforce each other's action in producing ataxia, euphoria, etc.

OUR EXPERT writes: Despite an exhaustive search I have found no reports on the effect of alcohol and barbiturates when used together on ataxia, euphoria, etc. I think in my original answer I might have been wiser to have used the word "synergism" rather than to have talked about "potentiation." The synergistic effect between ethyl alcohol and phenobarbitone has been well demonstrated experimentally by Jetter and Maclean.[1] When the maximum sublethal dose of one drug plus half that of the other was used, death was produced regularly. Similar fatal synergism is suggested by observation on three poisoning cases in human beings. Nevertheless Sandberg[2] has demonstrated a potentiative type of synergism between ethyl alcohol and six short-acting barbiturates—the degree of potentiation varying with the dose and the derivative.

REFERENCES

[1] *Arch. Path.*, 1943, **36**, 112.
[2] *Acta physiol. scand.*, 1951, **22**, 311.

Recurrent Parotid Enlargement.—Dr. M. SECKBACH (London, N.W.11) writes: Your correspondent ("Any Questions?" February 7, p. 348) asks whether there is any known relationship between menstruation and recurrent parotid enlargement. I am reminded of a case I saw 20 years ago which had previously been labelled "recurrent parotid enlargement." When I saw the patient she told me she had noticed a swelling, associated with tenderness, in the region of the parotid gland shortly after an abortion six years previously. This swelling subsided after a few days, but recurred at every menstruation. She had never noticed anything like that before the abortion. On examination I was able to feel a small soft nodule constantly present. There was no other pathological finding. Any lung or blood disease had been excluded and there was no evidence of calculus in the parotid duct. The fact that the swelling started after an abortion and had recurred with each menstruation for six years raised my suspicion of an accessory thyroid gland. Portions of this gland may be displaced during the course of development. The existence of a lingual thyroid and of small pieces of thyroid tissue at some distance from the normal thyroid gland between the tongue and the arch of the aorta is known. Puberty and pregnancy are among the predisposing factors of goitre. A minor swelling of the thyroid gland during or just before onset of menstruation, particularly in young girls, has often been observed. The thyroid gland was in its normal position in my particular case. An exploratory operation confirmed the diagnosis of an accessory thyroid. The small tumour consisted of thyroid tissue and had a fibrous capsule. The possibility of aberrant thyroid tissue has therefore to be borne in mind in the case mentioned by your correspondent.

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